JANUARY 11, 1999 $2.95

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TIME

LOTT'S IMPEACHMENT PLAN

SPECIAL ISSUE

THE FUTURE OF MEDICINE

How genetic engineering will change us in the next century

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We've cared for generations.

JANUARY 11, 1999

TIME

VOL. 153 NO. 1

THE WEEKLY NEWSMAGAZINE

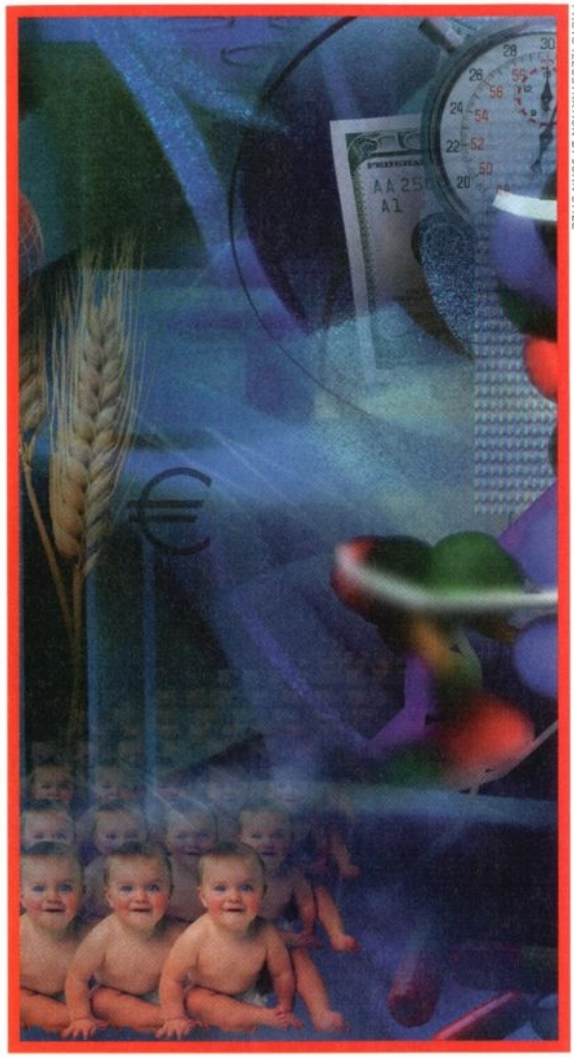
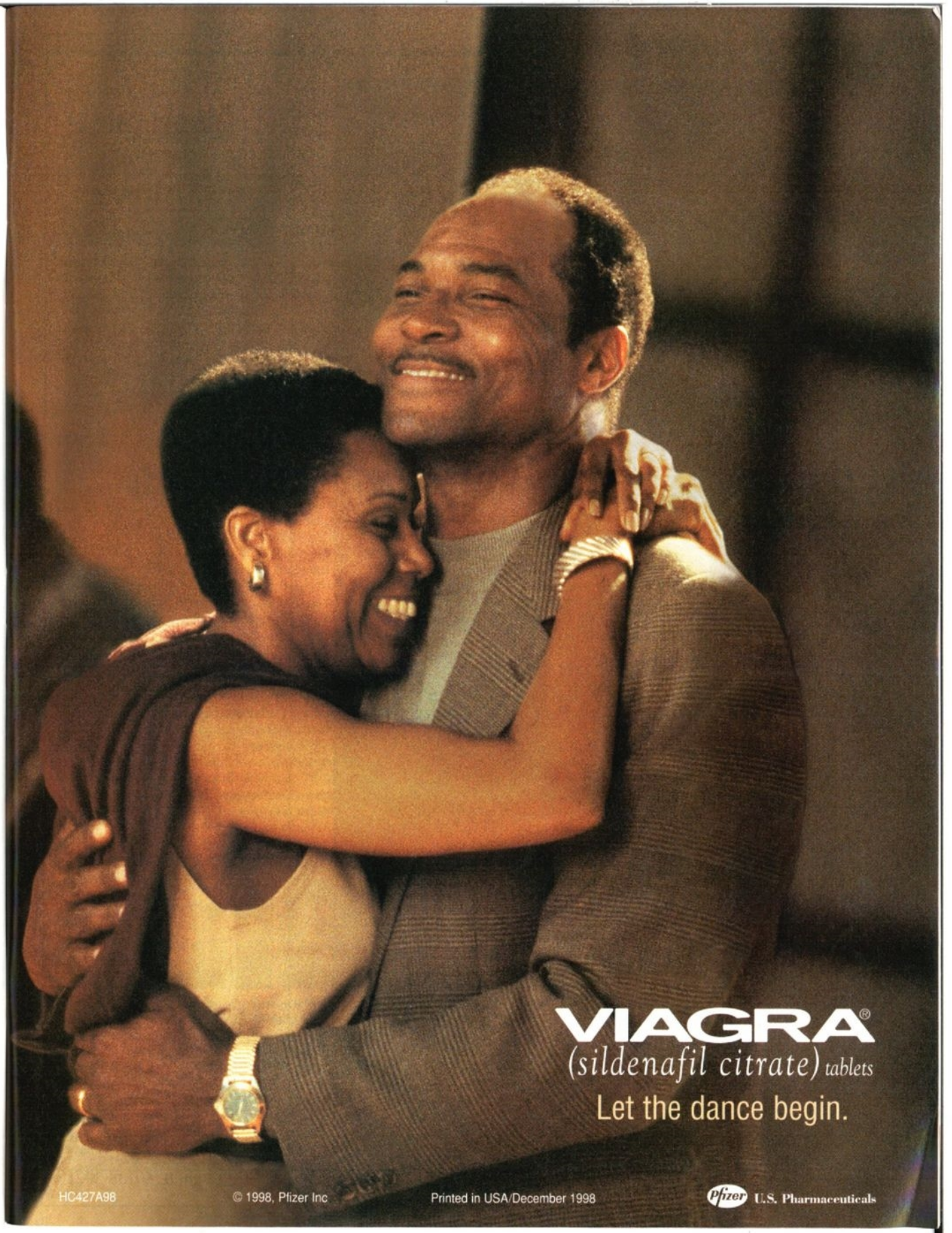


PHOTO-ILLUSTRATION BY JOHN STILL

COVER: *Illustration for* TIME *by Jerry LoFaro*

TIME (ISSN 0040-781X) is published weekly except for two issues combined into one at year-end and occasional special or double issues for $67.33 per year by Time Inc. Principal Office: Time & Life Building, Rockefeller Center, New York, N.Y. 10020-1393. Don Logan, Chairman, CEO; Joseph A. Ripp, Treasurer; Robert E. McCarthy, Secretary. Periodicals postage paid at New York, New York, and at additional mailing offices. POSTMASTER: Send address changes to TIME, P.O. Box 30601, Tampa, Florida 33630-0601. **For subscription queries, call Customer Service at 1-800-843-TIME between 7 a.m. and midnight EST, Monday through Friday; 8:30 a.m. and 7:00 p.m. EST, Saturday. For expedited service, call between the hours of 2:30 p.m. and 6:30 p.m., Tuesday through Thursday.**


VIAGRA®
(sildenafil citrate) tablets
Let the dance begin.
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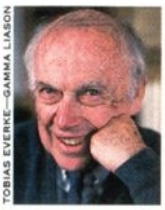
Printed in USA/December 1998
Pfizer U.S. Pharmaceuticals

CONTRIBUTORS


TED THAI FOR TIME


MARY ELMER-DEWITT

BARRETT SEAMAN and **PHILIP ELMER-DEWITT,** who co-edited this week's comprehensive 44-page report on the future of medicine, boast impressive résumés in such projects. Seaman, TIME's special-projects editor, has overseen two recent special issues on medicine and last October's look at a week in the life of a hospital. Elmer-DeWitt, TIME's science editor, has written cover stories on gene therapy and cloning. But when they began framing the topic of this issue, they realized they would need expert assistance. "We decided to focus on genetics, which is the area of research likely to have the greatest impact on how medicine is practiced in the future," says Elmer-DeWitt. "But it's a complex field that's moving quickly." The two editors invited a parade of working scientists from around the world to brief the staff members. "We were able to bring the whole group up to speed on state-of-the-art technologies and theories," says Seaman. The resulting effort, coordinated by Andrea Dorfman, chief reporter of the science section, offers an unblinking look at the promises, risks and eccentric personalities shaping the field. "There's plenty of good news here," says Seaman, "but we don't shy away from the sobering ethical questions."


TOBIAS EVERKE—GAMMA LIAISON

JAMES D. WATSON, who contributed an essay on why genetic engineers must ignore the naysayers and forge ahead, is famous even among those who barely made it through high school biology for his and Francis Crick's 1953 discovery that DNA molecules arrange themselves in a double helix. That breakthrough earned them a Nobel Prize and made it possible to trace at the molecular level how cells organize hereditary information. In October, Watson drove in from the Long Island, N.Y., Cold Spring Harbor Laboratory, where he has worked for nearly three decades, to speak to TIME's reporters and editors. Elmer-DeWitt used the opportunity to invite Watson to write the package's closing essay. "He's an icon of molecular genetics," says Elmer-DeWitt. "And unlike many scientists, he is a lucid and engaging writer."


MIKE THEILER—REUTERS

IAN WILMUT became the world's best-known embryologist in early 1997, when he and his team at Scotland's Roslin Institute announced that they had cloned a mammal, a lamb named Dolly, from the single cell of an adult sheep. But the science that produced Dolly also gave rise to disquieting questions that still rattle ethicists and policymakers. Managing editor Walter Isaacson met Wilmut at the annual Forstmann Little seminar in Aspen, Colo., last September and engaged him in a lively conversation on the ethics of cloning. "Wilmut expressed his concern that the breakthrough he had wrought would be used by others with no thoughtful moral or legal guidelines," says Isaacson, who promptly recruited Wilmut to write the essay on the subject that appears in this week's issue.

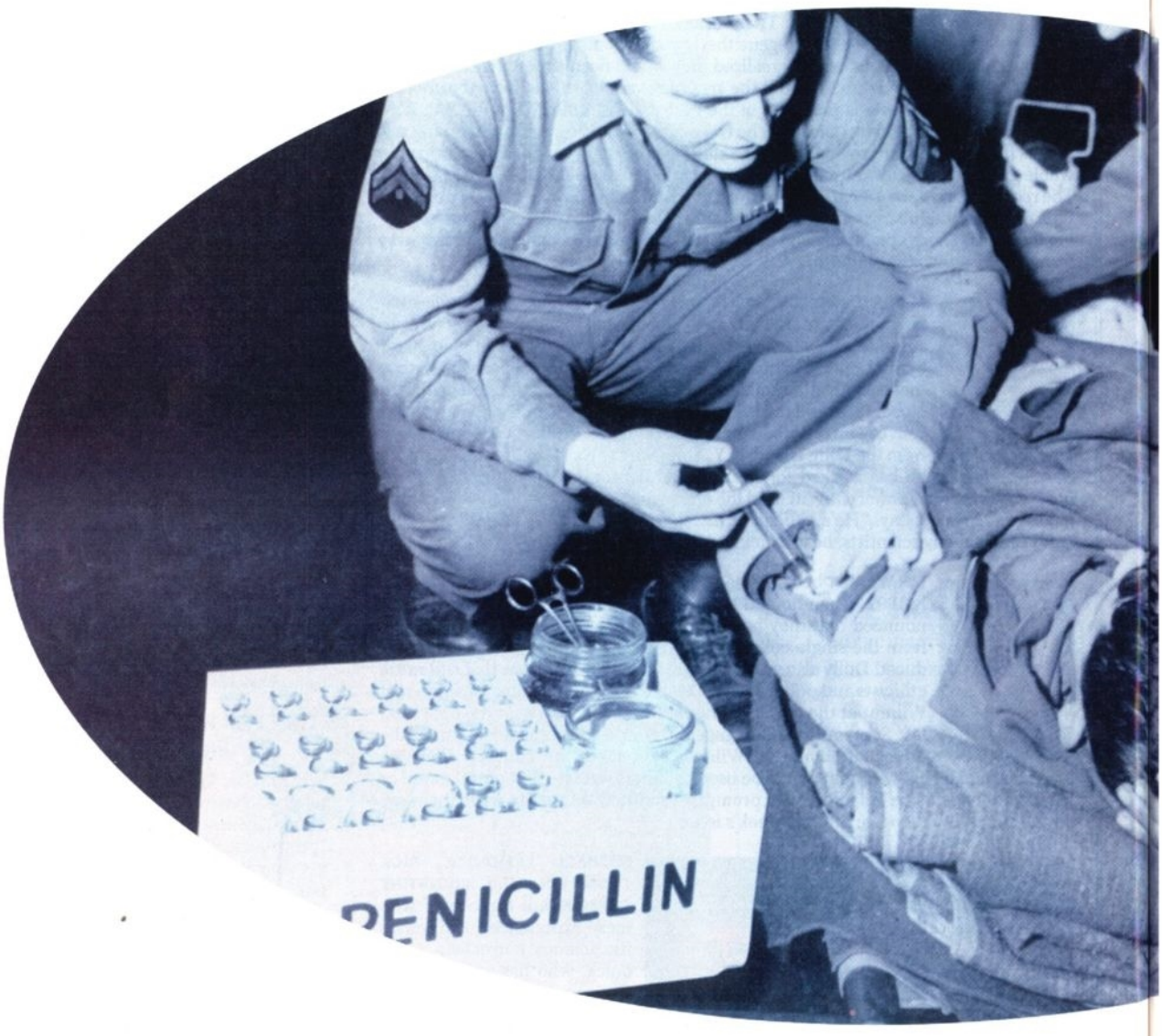

TED THAI FOR TIME


TERRY ASHE FOR TIME


MARIO RUIZ FOR TIME

MICHAEL LEMONICK, DICK THOMPSON and **CHRISTINE GORMAN** are three of TIME's most experienced and versatile science journalists. Lemonick, who has written cover stories on topics ranging from killer microbes to biblical archaeology, says the lead story on the race to map the human genome was particularly fascinating as it mixed pure science with human emotions. "When scientists tamper with the basic machinery of human existence," he says, "they can get very involved." A relative newcomer to molecular genetics, Lemonick was relieved to have Washington-based Thompson share the story's reporting and writing. Thompson, who has followed the field since 1980, made a special effort to get inside the laboratory—and the mind—of controversial gene hunter Craig Venter, whom he profiles in this week's issue. Meanwhile, senior writer Gorman was taking field trips to pharmaceutical research labs for her story on drug discoveries. "This is an exciting area to track," she says, "because gene research is revolutionizing this industry."

We have a history of caring.



1950

Terramycin, a broad-spectrum antibiotic, becomes the first pharmaceutical discovered by Pfizer and sold under the company label.

1952

Pfizer establishes an Agricultural Division devoted to animal health. Today, Pfizer is one of the world's largest producers of pharmaceuticals for animals.

1971

Pfizer dedicates more than 15% of sales to research and development.

1997

For the first time, Pfizer is ranked the world's most admired pharmaceutical company by *Fortune* magazine.

OUR HISTORY

1849

Immigrant cousins Charles Pfizer & Charles Erhart open a fine-chemicals company in a Brooklyn, N.Y. plant.

1868

Many of the surgical chemicals Union forces use during the Civil War are supplied by Pfizer.

1941

Pfizer discovers a method to mass produce penicillin, an event that alters medical history and Pfizer's future.

1944

Pfizer is the largest producer of penicillin and supplies 90% of the penicillin that goes ashore on D-Day in Normandy.

We're Pfizer.

We're the company founded in 1849 by two immigrants. We're the people who produced life-saving surgical chemicals used in the Civil War. We were the first to discover how to mass produce the world's first miracle drug—penicillin. It was our penicillin that saved so many lives on D-Day. Today, we're in the forefront in the war against depression, diabetes, cardiovascular diseases and countless other illnesses. We're intent on being the company that introduces more new medicines for more diseases than anyone else. For 150 years, everyone at Pfizer has come to work with the knowledge that we're not just in business, we're in business for life.

1998

Pfizer's roster of medicine grows with the launch of Trovan, a new antibiotic, and Viagra, the first oral treatment for erectile dysfunction.

1999

Pfizer celebrates its 150th anniversary. The company invests over two billion dollars annually in research and development, searching for tomorrow's medical miracles.

Pfizer 150

Life is our life's work.

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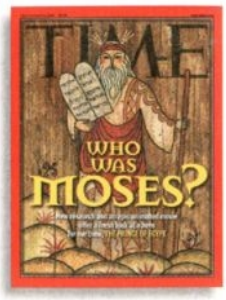
LETTERS



In Search of Moses

"Moses was hated in his day because he told the truth. If he lived in these dark times, he'd be twice as hated."

MARGIE J. PHELPS
Topeka, Kans.

IT WAS AMUSING TO SEE THE SCHOLARS going to great lengths trying to analyze Moses' life and legacy in your article "Who Was Moses?" [COVER, Dec. 14]. I was hoping to find at least one of your experts calling Moses what he really was—a general at war with a powerful enemy. Moses was more like Alexander the Great than the key religious figure he is purported to be. Moses had no qualms about asking God to visit upon his enemies the worst of suffering and disease, even death. His God was ruthless and vengeful. Just because Moses invoked God going into battle doesn't make him a respectable religious figure.

D. SREENIVASA RAO
North Andover, Mass.

PRACTICALLY, IT MAKES NO DIFFERENCE whether Moses existed or not. Most important is the symbolism of his leadership, enforcing the notion of a single God and fortifying faith among his people. Great leaders, like the one illustrated by the concept of Moses, effectively use spiritual assurance of a religious nature as a crucial weapon to restrain human aggressiveness and maintain unity.

ALBERT C. CUETTER
El Paso, Texas

THE STORY OF MOSES IS PURE BALONEY, AS are most of the stories in the Bible. It is incredible that in this day such stories are still being fed to innocent children.

PAUL H. BARLOW
Weddington, N.C.

ALMOST EVERY TIME YOU DO A PROFILE on a biblical figure you go to great lengths to explain and quote the views of liberal scholars and archaeologists. You should give equal space to the opinions of conservative scholars and archaeologists. TIME seems to have a mission of discrediting beliefs, because you do so little to present the other side.

ERNEST SCALABRIN
Northvale, N.J.

HOW CAN WE QUESTION MOSES IN AN AGE of Monica Lewinsky, Linda Tripp and Bill Clinton? We need someone we can look up to for moral and spiritual support. Moses in 2000!

TAE KIM
New York City

I WAS GLAD TO LEARN FROM YOUR ARTICLE on Moses that "movie directors have immortalized him." It is frightening to consider that were it not for Hollywood, Moses would be forgotten!

JOSEPH MORE
Cromwell, Conn.

Animating the Bible

JEFFREY KATZENBERG'S MOTIVES FOR creating the movie *The Prince of Egypt* must be judged over time [COVER, Dec. 14]. Was it Katzenberg or others at Disney who had the Midas touch for creating successful animated films? Assessing the box-office appeal of *Prince of Egypt* is a practical way of answering that question. Perhaps Katzenberg's contribution to improved understanding of the Pentateuch would be to allocate a portion of this film's profits to subsidizing independent scholarly research into the Old Testament characters. *The Prince of Egypt's* expected income would hardly be dented by funding a substantial annual Moses Prize.

DAVID W. FAULKNER
Bristol, England

IN HIS REVIEW OF THE MOVIE, RICHARD Corliss said it "sometimes looks starched, stodgy," and told readers that "any sort of irreverence would be out of place in this by-the-Book rendition" of the Old Testament. Maybe *The Prince of Egypt* does not fit the Disney mold. However, a story dealing with mass slavery, violence and pestilence does not lend itself to comedy. Films like this one give me hope. The time has come to honor children as an audience capable of understanding things beyond the comprehension of misguided reviewers.

SARA A. SCOTT
Laconia, N.H.

IT'S BAD ENOUGH THAT *THE PRINCE OF Egypt* has Pharaoh's wife, rather than daughter, rescuing the infant Moses. But to depict the Israelites as having built the pyramids? Come on! Cheops erected his massive stone piles centuries before Joseph was sold into slavery! Holy Writ says the Hebrew slaves "built for Pharaoh treasure cities, Pithom and Raamses," not pyramids.

ALFRED R. MATTHEWS
Huntsville, Ala.

RITALIN REDUX

Congratulations to TIME for the report on treating hyperactive youngsters [COVER, Nov. 30]. Exactly 30 years ago you published an article on the use of Ritalin. My letter to the editor, printed in your Nov. 8, 1968, issue, still seems timely and relevant.

Ann Martin (formerly Ann Nash)
Redstone, Colo.

Sir: Re "Those Mean Little Kids" [Oct. 18, 1968]: Heaven help us. If we ... resort to doping rather than coping with our children, can Aldous Huxley's Brave New World be far away? Ritalin now, Soma later.

(Mrs.) Ann Nash
Olathe, Kans.

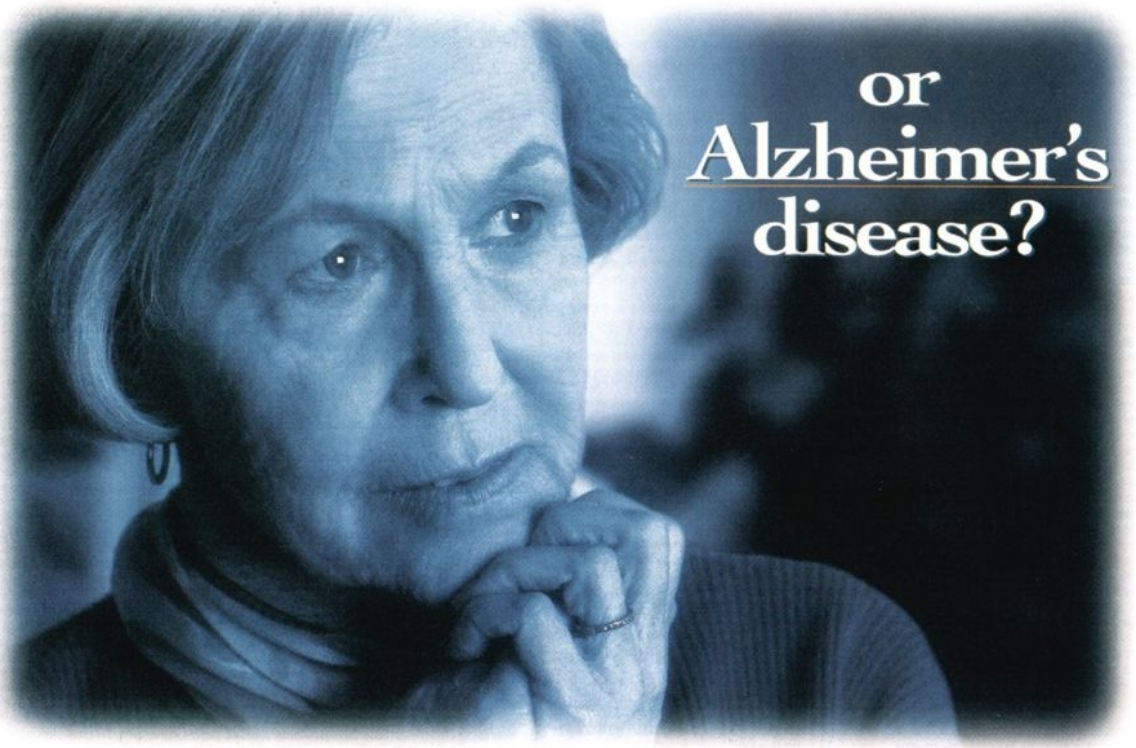
Taking the Economic Initiative

I WAS SO PLEASED TO SEE THE ARTICLE ON Madame C.J. Walker and her hair-care business in your report on the century's Builders and Titans [TIME 100, Dec. 7]. How much more difficult is it to succeed in business when you start out poor and uneducated? And how much more difficult when you're female and black? It is only after putting Madame Walker's accomplishments in the context of the harsh realities she endured and overcame that one can truly appreciate the magnitude of her success.

VIVIAN RANDOLPH, PRESIDENT
Madame C.J. Walker Enterprises Inc.
Indianapolis, Ind.

I WAS PLEASED TO SEE A MENTION OF MY former boss, Muriel ("Mickie") Siebert, in your Builders and Titans report. All professional women owe Siebert, the first woman to buy a seat on the New York Stock Exchange, a debt of grati-

Is it just forgetfulness...



• Memory loss • Asking repeated questions • Trouble using words

When signs like these begin to affect everyday life, they may not be a part of normal aging. They may be signs of Alzheimer's disease, an incurable, progressive illness that robs patients and their families of a lifetime of memories.

Today, however, the outlook for many is becoming more hopeful. ARICEPT® is a clinically proven, once-a-day prescription medicine available to treat symptoms in patients with mild to moderate Alzheimer's disease. Already, over 400,000 patients in the United States have begun ARICEPT® therapy.

ARICEPT® is well tolerated, but some people do experience side effects like nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and loss of appetite. In clinical studies, these effects were generally mild, temporary, and went away with continued ARICEPT® use; 2% of people taking ARICEPT® experienced fainting.

Only a doctor can evaluate symptoms such as forgetfulness and diagnose Alzheimer's disease. Speak to a doctor *today* about the benefits of ARICEPT® in treating Alzheimer's disease.

ONCE-A-DAY
ARICEPT®
(donepezil HCl)
5-MG AND 10-MG TABLETS

TODAY'S TREATMENT FOR ALZHEIMER'S DISEASE

To learn more, call toll-free today.

1-888-999-9616 ext. 91

Please see additional important product information on accompanying page.

People at risk for ulcers should inform their doctor.

ONCE-A-DAY
ARICEPT® (donepezil HCl) 5-MG AND 10-MG TABLETS
TODAY'S TREATMENT FOR ALZHEIMER'S DISEASE

ARICEPT® (Donepezil Hydrochloride Tablets)
Brief Summary—see package insert for full prescribing information. **INDICATIONS AND USAGE** ARICEPT® is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. **CONTRAINDICATIONS** ARICEPT® is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. **WARNINGS** ***Anesthesia:*** ARICEPT®, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. ***Cardiovascular Conditions:*** Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (eg, bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. Syncopal episodes have been reported in association with the use of ARICEPT®. ***Gastrointestinal Conditions:*** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, eg, those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. ARICEPT®, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea, and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®. ***Genitourinary:*** Although not observed in clinical trials of ARICEPT®, cholinomimetics may cause bladder outflow obstruction. ***Neurological Conditions:*** Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease. ***Pulmonary Conditions:*** Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **PRECAUTIONS Drug-Drug Interactions** ***Drugs Highly Bound to Plasma Proteins:*** Drug displacement studies have been performed *in vitro* between this highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. ARICEPT® at concentrations of 0.3-10 µg/mL did not affect the binding of furosemide (5 µg/mL), digoxin (2 ng/mL), and warfarin (3 µg/mL) to human albumin. Similarly, the binding of ARICEPT® to human albumin was not affected by furosemide, digoxin and warfarin. ***Effect of ARICEPT® on the Metabolism of Other Drugs:*** No *in vivo* clinical trials have investigated the effect of ARICEPT® on the clearance of drugs metabolized by CYP 3A4 (eg, cisapride, terfenadine) or by CYP 2D6 (eg, imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_i about 50 -130 µM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference. Whether ARICEPT® has any potential for enzyme induction is not known. Formal pharmacokinetic studies evaluated the potential of ARICEPT® for interaction with theophylline, cimetidine, warfarin and digoxin. No significant effects on the pharmacokinetics of these drugs were observed. ***Effect of Other Drugs on the Metabolism of ARICEPT®:*** Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of these inhibitors is not known. Inducers of CYP 2D6 and CYP 3A4 (eg, phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®. Formal pharmacokinetic studies demonstrated that the metabolism of ARICEPT® is not significantly affected by concurrent administration of digoxin or cimetidine. ***Use with Anticholinergics:*** Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. ***Use with Cholinomimetics and Other Cholinesterase Inhibitors:*** A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity studies of donepezil have not been completed. Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test. Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis). **Pregnancy** *Pregnancy Category C*: Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m² basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m² basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and a slight decrease in pup survival through day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers** It is not known whether donepezil is excreted in human breast milk. ARICEPT® has no indication for use in nursing mothers. **Pediatric Use** There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT® in any illness occurring in children. **ADVERSE REACTIONS Adverse Events Leading to Discontinuation** The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%. The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients were nausea (1% [5 mg] and 3% [10 mg] vs 1% [placebo]), diarrhea (<1% [5 mg] and 3% [10 mg] vs 0% [placebo]), and vomiting (<1% [5 mg] and 2% [10 mg] vs <1% [placebo]). **Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT®** The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT®'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue, and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT® treatment without the need for dose modification. There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day. See Table 1 for a comparison of the most common adverse events following one week and six week titration regimens. **Adverse Events Reported in Controlled Trials** The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 2 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT® and for which the rate of occurrence was greater for ARICEPT® assigned than placebo assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age. **Other Adverse Events Observed During Clinical Trials** ARICEPT® has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 116 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days. Treatment emergent signs and symptoms that occurred during 3 controlled clinical trials and two open-label trials in the United States were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving ARICEPT®. All adverse events occurring at least twice are included, except for those already listed in Tables 1 or 2, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: *frequent adverse events*—those occurring in at least 1/100 patients; *infrequent adverse events*—those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEPT® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the United States. **Body as a Whole:** *Frequent:* influenza, chest pain, toothache; *Infrequent:* fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness. **Cardiovascular System:** *Frequent:* hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; *Infrequent:* angina pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis. **Digestive System:** *Frequent:* fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; *Infrequent:* eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydypsia, duodenal ulcer, stomach ulcer. **Endocrine System:** *Infrequent:* diabetes mellitus, goiter. **Hemic and Lymphatic System:** *Infrequent:* anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia. **Metabolic and Nutritional Disorders:** *Frequent:* dehydration; *Infrequent:* gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase. **Musculoskeletal System:** *Frequent:* bone fracture; *Infrequent:* muscle weakness, muscle fasciculation. **Nervous System:** *Frequent:* delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; *Infrequent:* cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing. **Respiratory System:** *Frequent:* dyspnea, sore throat, bronchitis; *Infrequent:* epistaxis, postnasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring. **Skin and Appendages:** *Frequent:* pruritus; diaphoresis, urticaria; *Infrequent:* dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer. **Special Senses:** *Frequent:* cataract, eye irritation, vision blurred; *Infrequent:* dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes. **Urogenital System:** *Frequent:* urinary incontinence, nocturia; *Infrequent:* dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis. **Postintroduction Reports** Voluntary reports of adverse events temporally associated with ARICEPT® that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block, hemolytic anemia, hyponatremia, pancreatitis, and rash. **OVERDOSAGE Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.** As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT® overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature. **DOSAGE AND ADMINISTRATION** The dosages of ARICEPT® shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day. Controlled clinical trials indicate that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. Because steady state is not achieved for 15 days and because the incidence of such effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks. Whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference. ARICEPT® should be taken in the evening, just prior to retiring, and may be taken with or without food.

Table 1. Comparison of Rates of Adverse Events in Patients Titrated to 10 mg/day Over 1 and 6 Weeks

	No titration		One-week titration	Six-week titration
Adverse Event	Placebo (n=315)	5 mg/day (n=311)	10 mg/day (n=315)	10 mg/day (n=269)
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle Cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

Table 2. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving ARICEPT® and at a Higher Frequency Than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=355)	ARICEPT® (n=747)
Percent of Patients With Any Adverse Event	72	74
Body as a Whole		
Headache	9	10
Pain, Various Locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular System		
Syncope	1	2
Digestive System		
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and Lymphatic System		
Ecchymosis	3	4
Metabolic and Nutritional Systems		
Weight Decrease	1	3
Musculoskeletal System		
Muscle Cramps	2	6
Arthritis	1	2
Nervous System		
Insomnia	6	9
Dizziness	6	8
Depression	<1	3
Abnormal Dreams	0	3
Somnolence	<1	2
Urogenital System		
Frequent Urination	1	2

Revised September, 1998

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Printed in USA/January 1999

tude. Were it not for her tenacity, gumption and drive, we'd still be searching for the ladies' room at the exchange.

AVA SLOANE
Hoboken, N.J.

THE 20TH CENTURY IS INDEED THE American century, but how could your list of movers and shakers have just one non-U.S. resident? The inclusion of Sony's Akio Morita almost seemed like tokenism—not that I would deny his place in history. But what about the industrialists who set about restoring the economy of Western Europe after the ravages of World War II? What about the founders of some of the conglomerates in the rest of the world? It was not only the U.S. that influenced the economy of the 20th century.

PHILIP ANDREW QVIST
Gauteng, South Africa

THE STORY ON MONSTROUS HOUSES THAT tycoons build, focusing on Bill Gates' "high-tech haven," smacked of sour grapes. If Gates has wealth that he earned by hard work, let him enjoy it and spend it how he chooses. Don't resent it when people have amassed a lot of money through their labors. They deserve to live any way they want.

JAYANTHI DE ALWIS
Colombo, Sri Lanka

Inside Private Banking

IN YOUR REPORT ON CITIBANK'S CLOSE relationship with Raúl Salinas, brother of former Mexican President Carlos Salinas [BUSINESS, Dec. 14], there were a few points I did not understand. You said Raúl Salinas' wife, using an alias, carried cashier's checks to Citibank Mexico City. Since these were for very large sums of money, I should think someone in Citibank's private-banking unit would have asked immediately about the origin of that money. Further, you noted that once Citibank had the funds, "no documents linked that money to Salinas." That shows an extraordinary amount of trust on Salinas' part. How could he ever prove the money was his? The bank could have cheated him out of his money, and he could hardly go to the police if he were robbed.

JIM BUDD
Colonia del Valle, Mexico

YOU STATED THAT A STRONG REASON FOR not prosecuting Citibank for money laundering is that "no one wants to see a major American institution lose its banking license." So now we have huge banks like Citibank that are not only too big to fail but also too big to prosecute. If the facts warrant it, a bank should be prosecuted to the full extent of the law, and if the result is the loss of its license, so be it. Citibank should have considered the consequences from the beginning.

CHAD JONES
Studio City, Calif.

The Pinochet Conundrum

HUMAN-RIGHTS ADVOCATES AROUND THE world rightly rejoice at the idea that Chile's ex-President Augusto Pinochet Ugarte might be extradited to Spain [WORLD, Dec. 14]. If this occurs, Pinochet will be judged for past crimes. Heads of government should never get away with torture and murder. But unless an impartial international criminal tribunal is established with very clear rules and procedures, going after only certain dictators will be an arbitrary process. Also, if a nation approves a general amnesty for atrocities committed by one of its regimes, should a foreign judge be allowed to disrupt that nation's healing process? I don't think so. Otherwise, as Charles Krauthammer stated [VIEWPOINT, Dec. 14], a dictator's best protection will be never to give up power.

EDUARDO ZAYAS-BAZÁN
Miami

BRITAIN CHOSE TO IGNORE CHILE'S DEMocratically elected President Eduardo Frei's demands that Pinochet be returned to Chile and his fate be decided by the Chileans. After all, the alleged crimes did not take place in England or Spain but in Chile. Thus British liberals are telling a presumably sovereign nation that territoriality doesn't count, that Chile cannot be trusted with its own political affairs. Colonialism is back.

EDWARD KAUSEL
Cambridge, Mass.

THE DEFENDERS OF GENERAL PINOCHET show no scruples when making a case for this South American butcher. They tell us about taking into account "humanitarian reasons" for the immediate release of the dictator, as if humanitarian considerations played a role in the thousands of torture sessions that occurred in Chile during Pinochet's regime. The charges against Pinochet are most seri-

PERSON OF THE CENTURY

TIME 100

As the 20th century draws to a close, TIME will be honoring the remarkable person who, for better or worse, has had the most profound impact on the events of the past 100 years. As always, we are interested in hearing from our readers about who should be chosen. And as we gather ideas throughout 1999, we look forward to reading your nominations—many of which we will publish in the Letters section in the months ahead. Please write to us at Person of the Century, TIME Magazine Letters, Time & Life Building, Rockefeller Center, New York, N.Y., 10020. Or send us an e-mail at *letters@time.com*.

NOTHING BUT THE TRUTH


PHOTOFEST

Schumann-Heink

At the end of one of his columns [NOTEBOOK, Nov. 30], Jeff Greenfield told the story about the pompous judge and the smartass lawyer. The judge asks, "Counselor, are you trying to show contempt for this court?" The lawyer responds, "No, your honor, I'm trying to conceal it." That joke smelled familiar to a few readers; one attributed it to Sir Rudolph Bing, artistic director of the Metropolitan Opera, presumably during labor negotiations, but in fact it was crusading lawyer Vincent W. Hallinan who coined the phrase. However, the mention of opera does bring us to diva Jessye Norman. As we noted [PEOPLE, Nov. 30], she tried to sue a magazine that claimed that when she got wedged in a door and was advised to turn sideways, she retorted, "Honey, I ain't got no sideways." Readers were on her side of the lawsuit, but some knew other versions of the tale. "The real story concerned contralto Mme. Ernestine Schumann-Heink much earlier in this century," W.D. MacCallan of Savannah, Ga., informed us. "As the singer was struggling along a narrow path between the orchestra and the footlights, one violinist whispered, 'Sideways, Madame, sideways.' To which she huffily retorted, 'Mein Gott! I haff no sidevays!'" Gee, even the campy dialect seems a bit stale.

HEALTH

Ear Infections.
The more you know, the more you can help.

You've seen your child's symptoms. Crying all night. No appetite. Waking every hour or two, running a fever, tugging at little ears. Just when you thought you had it conquered for the season, your child's ear infection is back. Bacteria are often the culprits. Fortunately, antibiotics may help. But your role is also crucial. And the more you know about ear infections, the better prepared you are to help fight them.

What is an ear infection and why does my child keep getting them?

Otitis media, more commonly known as an ear infection, is an inflammation of the middle ear (the space just behind the eardrum), and is often caused by bacteria. It can affect one or both ears, typically occurs with, or just after, a cold, and is usually accompanied by fluid build-up within the middle ear.

Although ear infections are not directly contagious, the colds and other respiratory tract infections that often precede them are. That's why children in day care and nursery school settings get ear infections frequently.

If you suspect your child has an ear infection, call your doctor. If appropriate, your doctor will prescribe an antibiotic. Don't insist that your physician prescribe your child an antibiotic, because at times antibiotics are neither necessary nor appropriate.

Can ear infections cause hearing loss or speech problems?

Ear infections can sometimes cause temporary hearing loss as a result of fluid build-up in the middle ear. Since children learn to speak by listening to others, this can occasionally result in speech and language delays.

What are antibiotics and how do they work?

Antibiotics are medications that either kill bacteria or stop them from growing. They are commonly prescribed for bacterial infections involving the respiratory tract. There are many different kinds of antibiotics. The specific antibiotic and the type of infection it's being used to treat determine the number of days and the number of doses per day the antibiotic needs to be taken. Some antibiotics can be taken for five days, while others are taken for 10 to 14 days. Only your doctor can determine which is appropriate for your child's condition.

Are antibiotics good for fighting colds too?

No. Antibiotics don't work at all against viral infections such as the common cold or flu. Only your doctor can determine the type of infection your child has and whether an antibiotic is necessary.

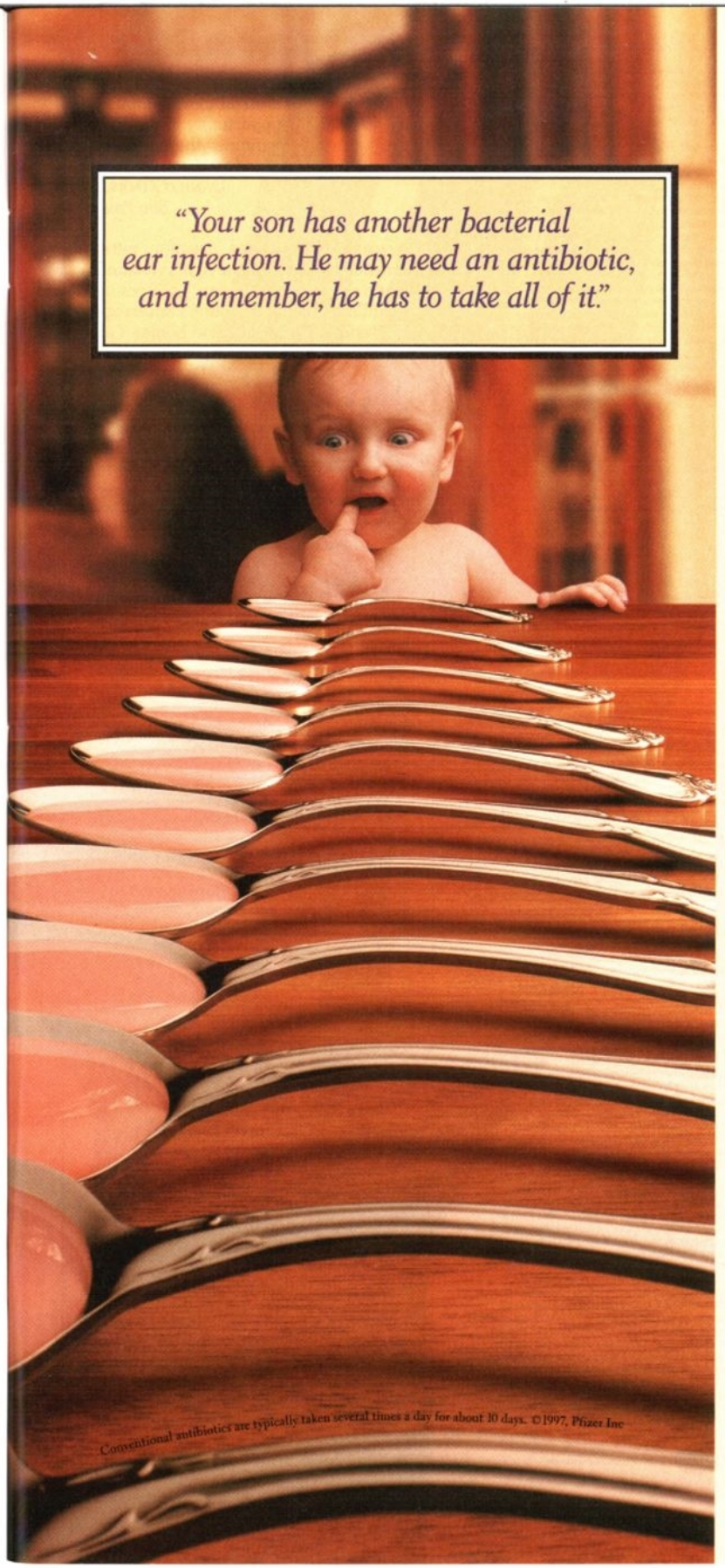
Why does my child have to keep taking antibiotics after he starts to feel better?

It is natural for your child to begin feeling better soon after starting antibiotics because they've begun their job of knocking out harmful bacteria. But just because your child's symptoms may be gone does not mean that the antibiotics have finished their work. If you stop antibiotics before the full course is finished, the infection may not be completely treated. Be sure to give your child the recommended medication as directed by the child's doctor.

Remember these tips.

- **If you suspect your child has an ear infection, see your doctor.**
- **Don't insist on a prescription for an antibiotic if your child has a viral infection, such as a cold or the flu.**
- **Complete the prescription, even after your child starts to feel well.**
- **Never share antibiotics with a sibling or anyone else. Throw away leftovers.**
- **Tell your doctor if your child is taking other medications.**
- **Follow your doctor's instructions carefully. Give doses on schedule for the number of days indicated.**
- **Remember, keep all medications well out of children's reach.**

Pfizer



Or ask your doctor about Zithromax.® Five days and you're done.

If your doctor is prescribing an antibiotic for your child's bacterial ear infection (acute otitis media), ask if Zithromax is right for your child.

THE ONLY ONCE-A-DAY FOR FIVE DAYS ANTIBIOTIC.

Unlike other antibiotics, you give Zithromax just once a day for five days. And five days are as effective as ten days of conventional therapy, because Zithromax continues to work for several days after the last dose.

Zithromax has a great cherry taste kids like, and is well tolerated. The most common side effects are diarrhea (2%), abdominal pain (2%), vomiting (1%), and nausea (1%). Although allergic reactions are rare, should one occur, discontinue this medication and contact your healthcare professional. See the brief summary on the next page for complete details.

ASK YOUR DOCTOR IF ZITHROMAX IS RIGHT FOR YOUR CHILD.

For more information on Zithromax and a free booklet on your child's language development and hearing, call 1-800-587-DAYS. Or visit us at www.KidsEars.com

Zithromax®
(azithromycin for oral suspension)
ONCE DAILY FOR 5 DAYS

Pfizer FIVE DAYS AND YOU'RE DONE.

ous. If he is not brought to trial, humanity will lose the opportunity to resolve a great misunderstanding: the confusion between ideology and fascism.

DANILO ZIMBRES
São Paulo

IMAGINE A CHINESE LEADER BEING arrested for past human-rights violations while shopping in London. Let's cut out meddling in another nation's sovereignty. Besides, I want peace at home—I am British and have a Chilean wife!

DAVID ALCOCK
Johannesburg

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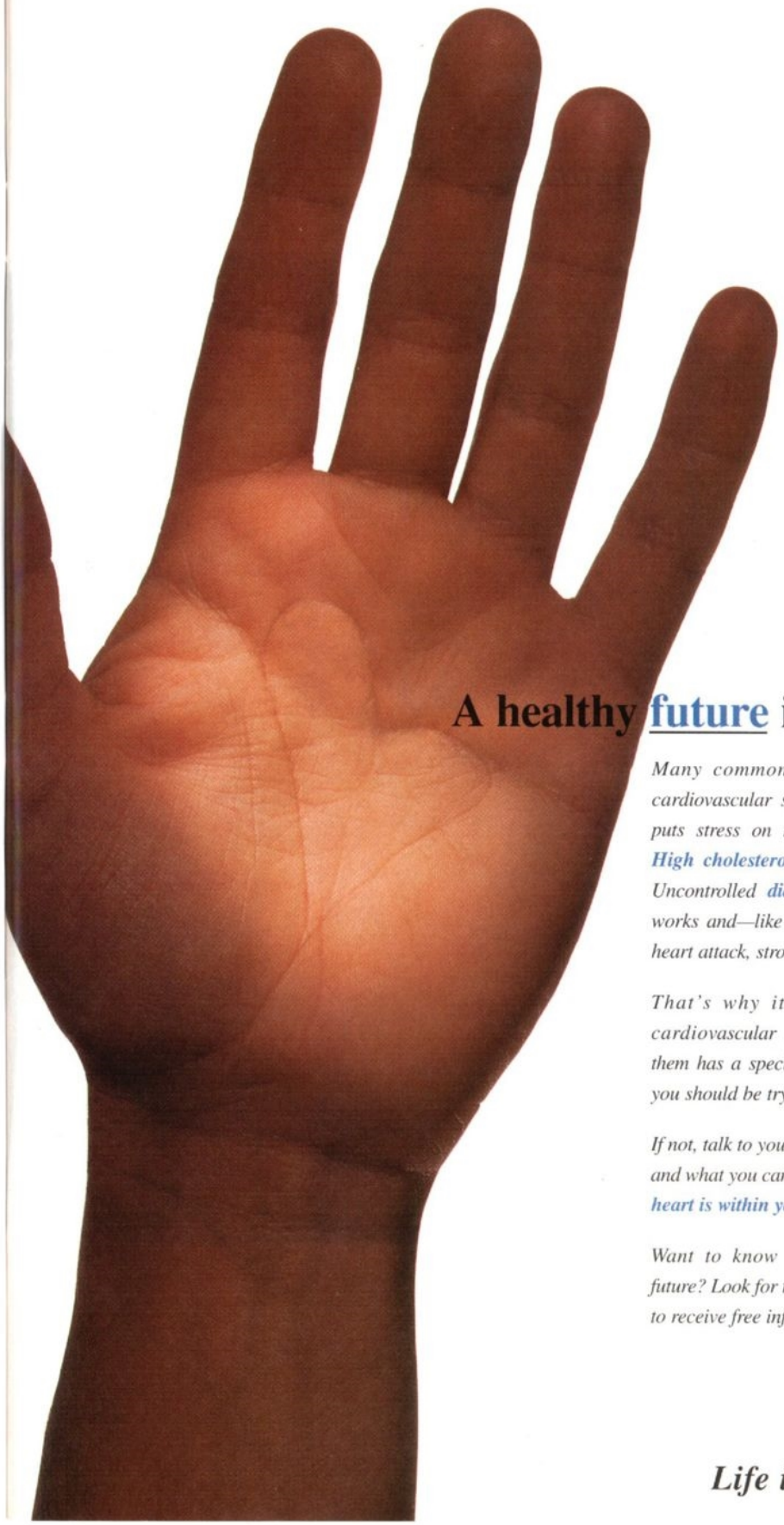
The World's Most Interesting Magazine



A healthy future is in your hands

Many common health problems can put your cardiovascular system at risk. ***High blood pressure*** *puts stress on the heart and other major organs.* ***High cholesterol*** *can clog important blood vessels. Uncontrolled* ***diabetes*** *affects how well your heart works and—like all of these conditions—can lead to heart attack, stroke, and severe kidney disease.*

That's why it's so important to keep these cardiovascular conditions controlled. Each one of them has a specific treatment goal, an actual number you should be trying to reach. Do you know yours?

If not, talk to your doctor; find out what your goals are and what you can do to reach them. ***Because a healthy heart is within your grasp today.***

Want to know more about your cardiovascular future? Look for the reply card located in this magazine to receive free information about these conditions.

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We mend broken hearts.

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We're Pfizer.
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And that's why we
believe we're on a path
to introduce more
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for more diseases
than anyone else.
At Pfizer, we know
in our hearts, the
only thing incurable
is our passion.

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We bring joy back to life.

We're Pfizer.
We've developed a medicine to fight a disease that keeps millions of people from leading normal lives—depression.
Last year, we spent over two billion dollars on research looking for cures for depression and other major diseases.
That's why we believe we'll introduce more new medicines for more diseases than anyone else. We know in our hearts the only thing incurable is our passion.

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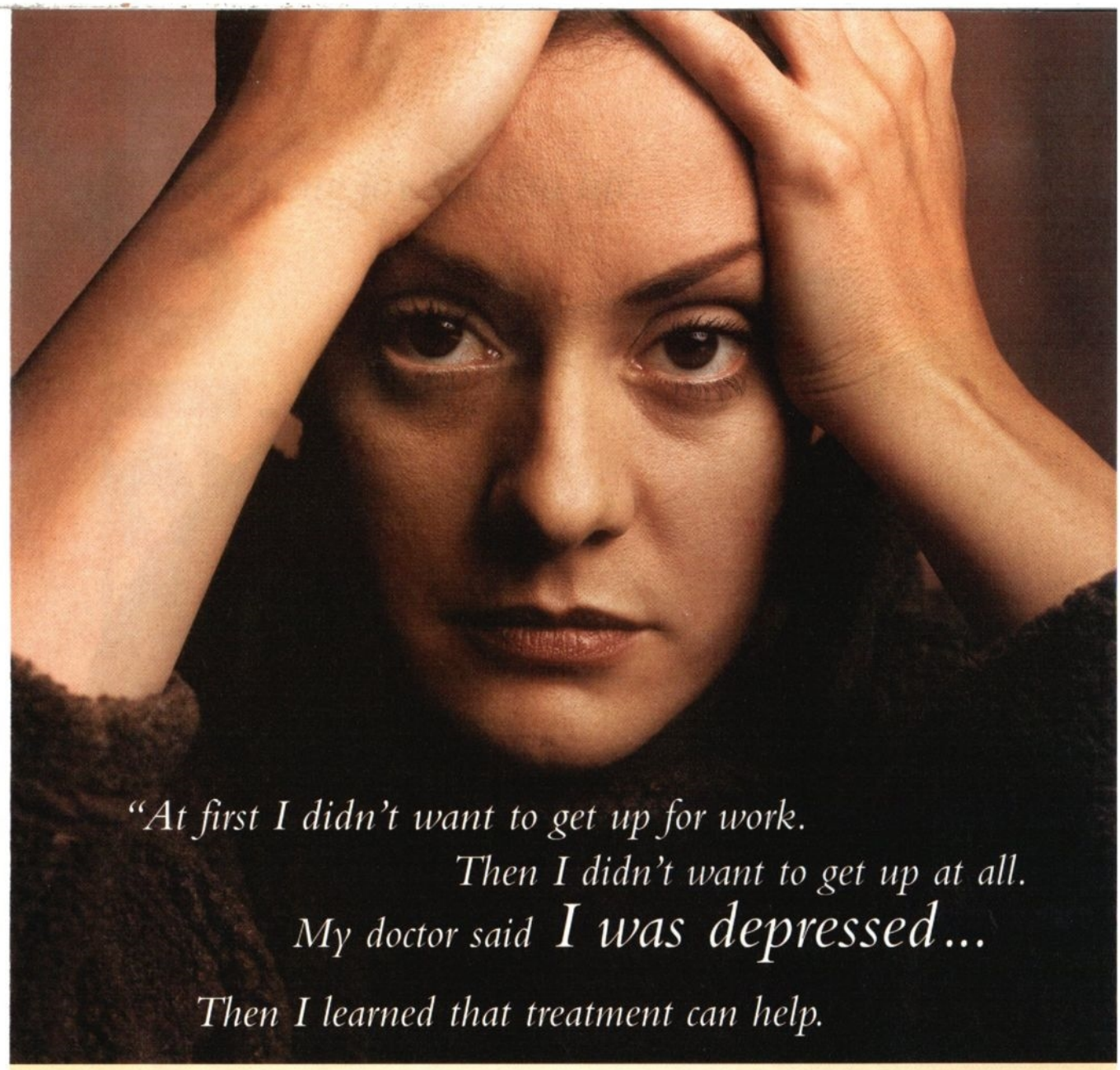


Now, I'm feeling better."

About 1 in 6 Americans will experience depression in their lifetimes. Depression is a condition that can affect people's jobs, families, and lives. But there is hope. Treatment is available—psychological therapy and antidepressant medicines are among the options that can help relieve depression. In fact, it has been shown that most people who receive treatment improve. Through patient education and research and development of drug therapies, Pfizer is helping millions of people realize that depression can be overcome.

If you'd like to learn more about depression, please call your doctor. For free, confidential brochures about depression, its symptoms, and its treatment, please call: **1-888-549-9422**.
www.depression-info.com

Life is our life's work Pfizer

VERBATIM

"I found Monica warm and intelligent and very open. I told her, 'You are very alive.' And she said, 'Maybe that was the appeal.'"

BARBARA WALTERS,
after meeting with Monica Lewinsky

"I like Bill Clinton. Do I think he's a total idiot? Yes."

HAROLD ICKES,
former White House deputy chief of staff

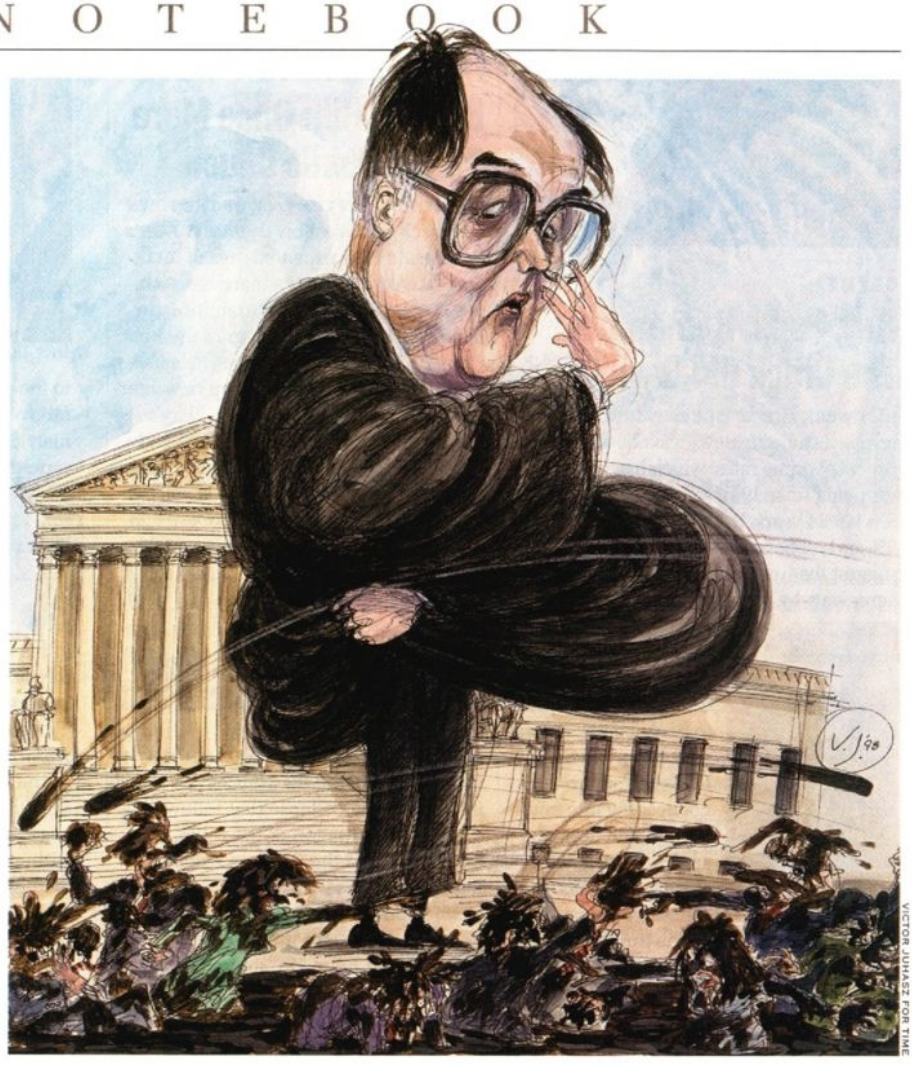
"I now have a 7-year-old boy and a 9-year-old boy, so all I can say is, I apologize. Now I know what you guys were talking about."

MATT GROENING,
creator of The Simpsons, *responding to complaints that Bart Simpson is a bad role model*

"Let bygones be bygones."

KHIEU SAMPHAN,
a former Cambodian head of state under the Khmer Rouge, after being promised amnesty from prosecution for genocide. Three days later, Prime Minister Hun Sen said Samphan and another defector may have to stand trial

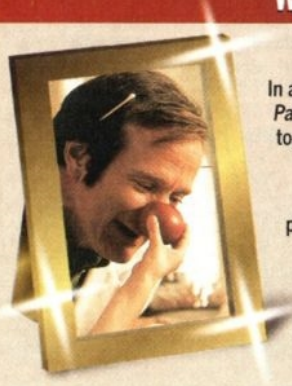
Sources: Walters (*TV Guide*); Ickes, Groening (New York *Times*); Samphan (Washington *Post*)



VICTOR JUHASZ FOR TIME

HEY! CAREFUL! THIS IS MY GOOD ROBE! Chief Justice William Rehnquist descends this week from his rarefied perch at the court to referee the capital's long-running ickfest. So why should he emerge unsullied when no one else has?

WINNERS & LOSERS



MELINDA SUE GORDON—UNIVERSAL

ROBIN WILLIAMS
In a contest of treacly movie ideas, *Patch Adams*' laughter-heals-pain tops *Stepmom's* love-your-enemy

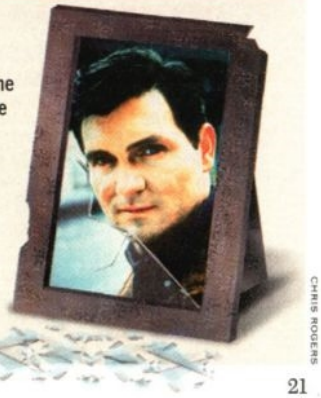
GARY ANDERSON
Vikings kicker sets record with perfect season. Still less famous than Bobby Boucher

THE INTERNET
Ten guys buy gifts online, and the NASDAQ explodes. Who owns *suckerventurecapitalists.com*?

KEVIN WILLIAMSON
Attractive teens! Hilfiger tie-ins! Still, *The Faculty* bombed. Now the *Scream* guy's got to learn to write

THE NBA
Last-minute settlement or no, pro hoops are in trouble. And we know Michael can't hit 70 taters

OUTDOORSY CEOS
Branson falls; Ellison survives deadly yacht race. Steaks and martinis are sounding healthy



CHRIS ROGERS

CRIME

Hey, Pops, Remember The Crack Old Days?

LAST WEEK THE JUSTICE DEPARTMENT released stunning news: violent- and property-crime rates, which have been dropping since 1991, are at their lowest level in 24 years. In 1997, murder dropped 8% and robbery fell 17%; early 1998 figures suggest the trend continues. Experts can't agree on why, citing factors from better policing to a booming economy. But one of the most fascinating developments seems to be that crack is now your father's drug. Users are maturing, if not heading into middle age, and dealers are less aggressive in recruiting youths, who tend to be turned off by crack's devastation (and more interested in the trendier, mellower highs of drugs like heroin). And the business has become more, well, mature as turf wars have been decided and trade has shifted from street sales to indoor client-list transactions. Then there's the bottom-line dictum offered by an expert: "Killing is bad for business." —**By Tamala M. Edwards**


JOE TABACCA—AP

Crack smoker

THE FIRST COUPLE

Bill and Hill: Once More On the Public Couch

IN WASHINGTON THE TALK OF THE TOWN this week will probably be ***VANITY FAIR'S*** look inside the tormented saga of **BILL** and **HILLARY CLINTON'S** marriage. **GAIL SHEEHY'S** 21-page report examines the psychological underpinnings of the First Couple's frequently anguished relationship. Among the highlights is a rare interview with Dorothy Rodham, Hillary's mom, who sheds light on the First Lady's seemingly superhuman stoicism: "She is a very sensitive person. But she is able not to overemotionalize it ... She doesn't go into one of these horribly overwrought kinds of tizzies." Adds Mom: "That's one thing I never did, either." Sheehy reports that the post-Monica healing process is far from over, quoting a source close to the couple who says Hillary has yet to forgive Bill fully. Sheehy's verdict on the marriage: If everyone is addicted to something, as the President has said, "Hillary's addiction is Bill. He is her only rebellion, the one thing she can't logically explain." —**By Flora Tartakovsky/New York**


J. SCOTT APPLEWHITE—AP

First Couple

RUSSIA

If You Think Boris Has It Tough . . .

RUSSIA'S ECONOMIC FREE FALL HAS NOT been kind to **MIKHAIL GORBACHEV.** First, in the banking collapse that followed last August's devaluation of the ruble, he lost—as he told the German magazine *Bunte*—his life savings of some $80,000. Then the Pizza Hut in Moscow that he made world famous in a TV commercial last year closed its doors. Now he's trying to make a little scratch and regain a measure of respect at home—where the vast majority of his compatriots continue to revile him for causing their present woes—with the latest volume in his post-Politburo oeuvre. Titled *Thoughts on the Past and the Future,* the 300-page "textbook" consists of the former General Secretary's deep thoughts on his country and the 20th century as the millennium approaches. Although Columbia University Press is to publish an English-language edition in 1999, Gorby has little hope for redemption at home. The Russian-language run of *Thoughts* is embarrassingly small: just 10,000 copies have been printed. And although the book costs only about $1, fewer than 100 of his die-hard groupies turned up last week at a gala press conference to grab the first copies. —**By Andrew Meier/Moscow**


MICHAEL EVSTAFIEV—REUTERS

Gorbachev

THE DRAWING BOARD

Cartoon by Ted Rall for TIME

999: That Was The Year That Was

ANYONE WHO ANTICIPATES ARMAGEDDON in 12 short months might like to remember—we've been here before. What difference 1,000 years make:

WORLD LEADERS

999: Pope Sylvester II is accused of sodomy, sorcery, worshipping idols and raising the dead

1999: William Jefferson Clinton is accused of perjury and obstruction of justice

CULVER PICTURES

CYNTHIA JOHNSON FOR TIME

MILLENNIAL CONCERNS

999: Impending Day of Judgment

1999: Impending Y2K bug

BIGGEST NEW YEAR'S EVE BLOWOUT

999: Thousands pack St. Peter's Basilica in Rome to witness the end of the world

1999: Thousands pack Times Square in New York City to witness the dropping of the new Waterford crystal ball

SOCIAL UPHEAVAL

999: Rise of new class of armored knights

1999: Rise of new class of techno-geeks

MASS MOVEMENTS

999: Entire nation of Iceland converts to Christianity

1999: Entire nation of moviegoers awaits *Star Wars* prequel

URBANO DELVALLE

The Y2K Commercial Bug

WANT TO MAKE YOUR MARK on the millennium? Better get in line. The U.S. Patent and Trademark Office has been inundated with more than 1,400 applications for millennial trademarks, which could lead to some serious endorsement conflicts at your next New Year's Eve party: Do you reach for the official champagne of the millennium (Korbel) or the official martini (Beefeater)? Our guide to the clash of the trademark titans:

PRODUCT	CONTENDER	VS. CONTENDER	OUR WINNER
BEER	**MILLER:** The Official Sponsor of the Millennium	**COORS:** The Official Beer of Y2K	Who wants to drink a brew that reminds you of a computer virus? It's Miller-ennium time!
CANDY	**M&M's:** The Official Candy of the Millennium	**MARS:** The Official Chocolate of the New Millennium	The M's have it in an intracompany battle—if only because their name spells out 2000 in Roman numerals
AIRLINE	**UNITED AIRLINES:** Official Airline of the Millennium*	**ALASKA AIRLINES:** Official Airline of the Millennium*	As a scary place that most people haven't been to yet, Alaska is more appropriate
FOOD	**UNCLE BEN'S:** The Food of the Millennium	**BOCA BURGER:** The Official Burger of the New Millennium	Sorry, Uncle, plain rice is the food of the past millennium
PROSAIC OBJECT	**ACME BRICKS:** The Official Brick of the Millennium	**ANGELO BROTHERS:** The Official Ballast of the New Millennium	After all those Road Runner cartoons, who could resist Acme?

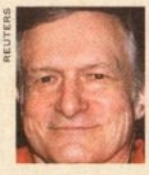
(*trademark pending)

60-SECOND SYMPOSIUM

PARDEE HARDEE
In 1982 Prince sang the soon-to-be-unavoidable lyric, "So tonight I'm going to party like it's 1999." Beyond that he offered no explanation. With the year finally upon us, we asked legendary revelers to tell us: How does one party like it's 1999?

BOB D'AMICO—ABC

DICK CLARK, Dorian Gray-ish New Year's Eve host: "The ideal way is to be with friends and family in a very familiar surrounding. Put the TV on as wallpaper in the background. I will keep you apprised of the time and the weather. Don't wallow on the bad side. Look forward to the good side, and be glad you are there to see tomorrow."



REUTERS

HUGH HEFNER, editor in chief of *Playboy*: "The party theme has a whole new meaning as we approach the new millennium. 1999 happens to be the Year of the Rabbit. We have a touring black bus that will look for that one special Playmate for the 2000 issue. We expect to interview and photograph 10,000 women. Work, work, work. Somebody has got to do it."

KATHY WILLENS—AP

HUNTER THOMPSON, journalist: "The police determine who whoops it up on New Year's Eve '99 and who doesn't. Law-enforcement wisdom anticipates chaos, curfews and riots. Criminals will run amuck. Misinformed SWAT teams will attack the guilty and innocent alike. Professional advice says stay home, lock doors, douse lights, don't answer the phone. Happy New Year."

CALVIN TRILLIN

Two for the Low Road

I HAVE GATHERED FURTHER EVIDENCE FOR THE VIEW that there are conflicting strains in the public's response to the current and presumably permanent scandal: most Americans deplore what Larry Flynt is doing and, at the same time, hope he comes up with something truly dreadful on Tom DeLay.

I did my own polling on that one—three adults, chosen at random toward the end of Christmas dinner.

The margin of error might have been affected by the first respondent's insistence on making a speech to all assembled about Robert Livingston's nearly attaining the speakership, an office that is third in the line of succession. "Say what you want to about Larry Flynt," the first respondent declared, "but if Livingston hadn't been exposed and Bill Clinton had been forced out of office, we could have had an adulterer a heartbeat away from the presidency."

Recently, when ABC's Sunday chat show from Washington clicked into the now ritualistic lamentations made by the Sabbath Gasbags about the politics of personal destruction, William Kristol, citing victims who are all Republicans, said that a willingness to use politicians' adulterous behavior against them was, in fact, found exclusively among forces of the left. The other 'bags found this statement unremarkable; somehow, the name Richard Mellon Scaife did not leap to mind.

Nor, for that matter, did Lucianne Goldberg or the *American Spectator* or the Washington *Times*, the Rev. Moon's contribution to the free marketplace of ideas, which printed evidence of Colorado Governor Roy Romer's extramarital relationship for reasons that have been lost to history. Nor did Tom DeLay, who now warns Senators not to vote on impeachment until they visit a locked room in the House office building for a glimpse of some juicy stuff that meets his standards of evidence even if it fell short of Kenneth Starr's. (Once dismissed by the snobs as an exterminator from Houston, DeLay has assumed the image of a dirty-postcard salesman from Tangier.)

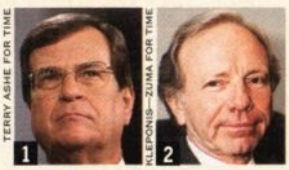
MATTHEW MARTIM FOR TIME

No, the sheet inspectors are on both sides. In fact, you could argue that Flynt and Scaife are just Democratic and Republican versions of the same person: neither is troubled by scruples, but the Republican, like those Republicans we saw on the House Judiciary Committee, is tidier and seems to have a lot less fun. In order to finance the Arkansas Project, an effort to find something dirty on Bill Clinton, Scaife coughed up roughly the same sort of money that Flynt offered in the advertisement he took to flush out bimbos with Republican leanings. Scaife was using tax-free foundation money, which simply reflects the fact that Republicans tend to be better at personal finance—although, now that I think of it, maybe Flynt can prove to the IRS that for a man in his line of work, payment for dirty information is a legitimate business deduction.

In fact, now that TIME's cover on Clinton and Starr has established the possibility of having yin-and-yang Men of the Year, we might look forward next year to having Larry Flynt and Richard Mellon Scaife. They would be presented as symbols of the enduring two-party system that's at the heart of our democracy. ■

CLICHÉ WATCH

POP QUIZ Think you're prepared for the President's upcoming impeachment trial? Take this test: match the Senator to his most frequently used media sobriquets and fun facts!



1. Trent Lott
2. Joseph Lieberman
3. Robert Byrd
4. Orrin Hatch
5. Daniel Patrick Moynihan

A. Stiff-necked Mormon elder; wearer of SAVE THE CHILDREN ties; a friend of Ted Kennedy's

B. Grandfatherly figure known for strict interpretation of the Constitution; tweedy; has clashed with Clinton in the past; Hell's Kitchen–raised

C. Self-appointed Senate historian; self-appointed guardian of senatorial prerogatives; known for his regal airs and bringing home the bacon

D. Never a hair out of place; former Ole Miss cheerleader who wins perfect ratings from conservative organizations; owlish partisan who honed leadership techniques alongside Newt Gingrich

E. A conscience of the Senate; longtime Clinton ally in the "New Democrat" movement; the Senate's only Orthodox Jew; a moralist with chutzpah

Answers: 1-D, 2-E, 3-C, 4-A, 5-B

MILESTONES

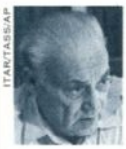

AP

DIED. MIKE McALARY, 41, tabloid columnist; of colon cancer; in New York City. Over the course of his career, the pugnacious, Pulitzer-prizewinning journalist wrote extensively—and often empathically—about the city's police for the New York *Daily News* and the New York *Post*. But he was no apologist: in 1997 he broke the story of a brutal police beating of a Haitian immigrant.

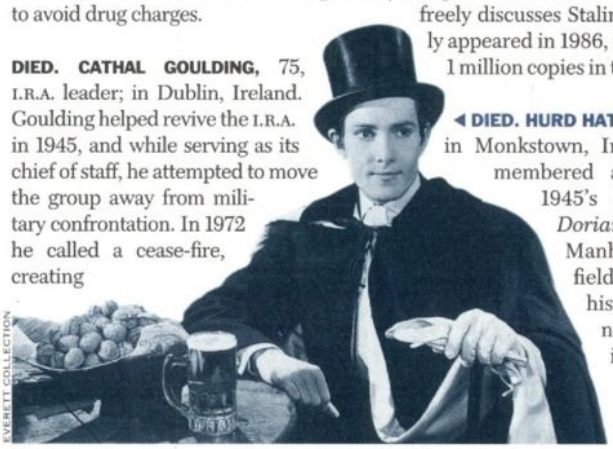
DIED. ANITA HOFFMAN, 56, social activist; of breast cancer; in San Francisco. Wife of the late Yippie Abbie, Hoffman joined her husband in some of his more outlandish activities, such as disrupting trading at the New York Stock Exchange by showering the floor with money. She also supported him for years while he hid from the police to avoid drug charges.

DIED. CATHAL GOULDING, 75, I.R.A. leader; in Dublin, Ireland. Goulding helped revive the I.R.A. in 1945, and while serving as its chief of staff, he attempted to move the group away from military confrontation. In 1972 he called a cease-fire, creating a split between his Official I.R.A. branch and the Provisional I.R.A., which sought continued armed strife.

DIED. JEAN-CLAUDE FOREST, 68, comic-strip artist; near Paris. Best remembered as the creator of the sci-fi cheesecake character Barbarella, he also designed the sets for the 1968 Jane Fonda film.


ITAR-TASS/AP

DIED. ANATOLI RYBAKOV, 87, Russian author; in New York City. Rybakov started writing stories part time while driving a truck. His children's book *The Dirk*, published in 1950, was an immediate success and admired by Stalin. On the other hand, it took years for him to get his epic novel *Children of the Arbat* published. When the work—which freely discusses Stalin's terrors—finally appeared in 1986, it sold more than 1 million copies in the Soviet Union.


EVERETT COLLECTION

◀ **DIED. HURD HATFIELD,** 80, actor; in Monkstown, Ireland. Best remembered as the lead in 1945's *The Picture of Dorian Gray*, the Manhattan-born Hatfield was famed for his arrogant manner. He appeared in such movies as Jean Renoir's *Diary of a Chambermaid*.

NUMBERS

$2.6 billion Total online shopping sales for 1997

$5 billion Estimated online shopping sales for the holiday season, 1998

$118 billion Total Wal-Mart sales for 1997

$15.4 billion Wal-Mart's current market capitalization

$72 billion AOL's current market capitalization

6 million Estimated number of visitors to the Eiffel Tower in 1998—a new record

6 million Estimated number of visitors to Disney's Animal Kingdom, Florida, in its first year

BOB HAMBLY FOR TIME

18,210 Total number of murders in the U.S. during 1997

25 Number of years since violent-crime rates have been this low

37 Estimated percentage of crimes that are reported to the police

Sources: Interpublic Group of Companies, Jupiter Communications, New York *Times*, Associated Press, FBI, Bureau of Justice Statistics

TIME CAPSULE

Back when a certain intern was still a junior at Lewis and Clark College, the Whitewater scandal broke. Attorney General **JANET RENO** *was authorized to appoint a special counsel:*


CYNTHIA JOHNSON FOR TIME

Clinton told advisers, "I want to get on with the business of my presidency," and gave the go-ahead for a special counsel ... But there are questions about the special counsel. Who will be chosen? Reno's only answer was someone "ruggedly independent" ... How broad or narrow will the probe be? Said Justice Department spokesman Carl Stern: "We are not going to tell the special counsel what to investigate. He or she is going to tell us." The difference could be crucial. An inquiry focused narrowly on Whitewater ... might be concluded speedily but be open to charges of inadequacy. A broader investigation could turn into a fishing expedition lasting years ... Obviously no one can predict the outcome of the special counsel's probe. The dealings are so complex that it is difficult even to summarize the suspicions they arouse ... But on another level, the investigation concerns the much larger issue of whether a President and First Lady can be trusted to obey the law and tell the truth.

—TIME, Jan. 24, 1994

By Tam Gray, Daniel Levy, Lina Lofaro, Joel Stein, Flora Tartakovsky and Chris Taylor

We're at home all over America.

SELF-MEDICATION

We're Pfizer. We not only make some of the world's most widely prescribed pharmaceuticals, we also make some of the most popular over-the-counter treatments found in American homes. In other words, Pfizer may be famous for the latest innovative new drugs, but one look in your medicine cabinet will tell you, we've actually been a friend of the family for years.

Pfizer

Life is our life's work.

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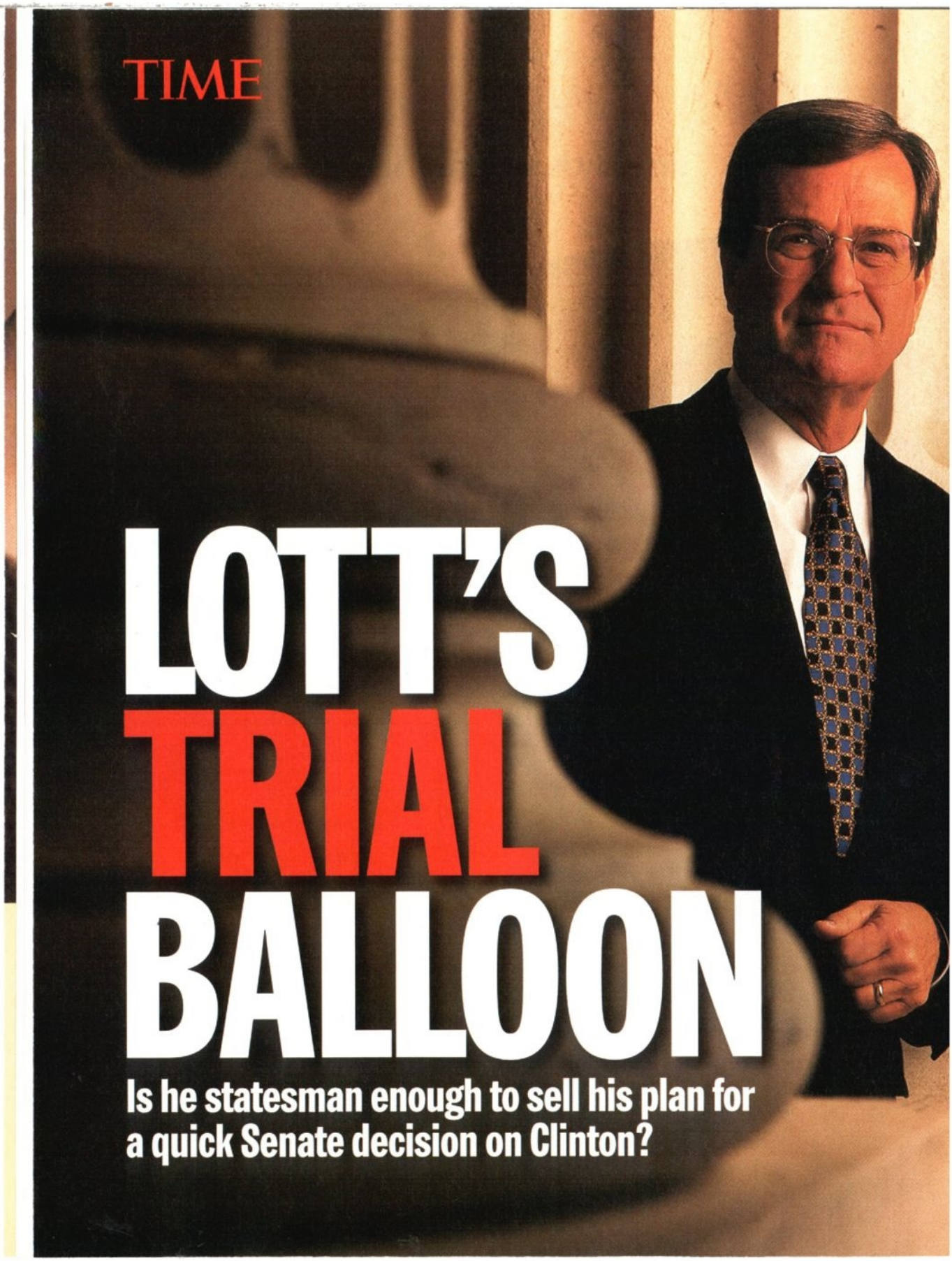
TIME



LOTT'S TRIAL BALLOON

Is he statesman enough to sell his plan for a quick Senate decision on Clinton?

J. SCOTT APPLEWHITE—AP

MEETING OF THE MINDS The majority leader, left, at the Capitol in quieter times, has a plan that Clinton, above, at Renaissance Weekend in South Carolina, could live with

JOHN CHIASSON—GAMMA LIAISON FOR TIME

By JAMES CARNEY and JOHN F. DICKERSON

SUSAN COLLINS, THE JUNIOR Senator from Maine, was sifting through a pile of Christmas cards at her home in Bangor one morning last week when the phone rang. "Hello, Susan!" said the smooth baritone voice on the other end of the line. It was Trent Lott, the Senate majority leader, calling from his home in Pascagoula, Miss., and wanting to talk about the biggest issue to confront the Senate in a generation: the impeachment trial of President Clinton. Hearing from Lott was a relief to Collins, a moderate Republican in a Democratic-leaning state where the President remains popular. It was even more of a relief to hear his responses. When Collins said she wanted the trial to start soon—in the next two weeks—and to end quickly, Lott agreed with her. And when Collins said she didn't want the impeachment debate to become a food fight as it had in the House, where Republicans came across as hell-bent on forcing Clinton from office, Lott agreed again. He may not have addressed all her concerns, but, says Collins, "I was really pleased."

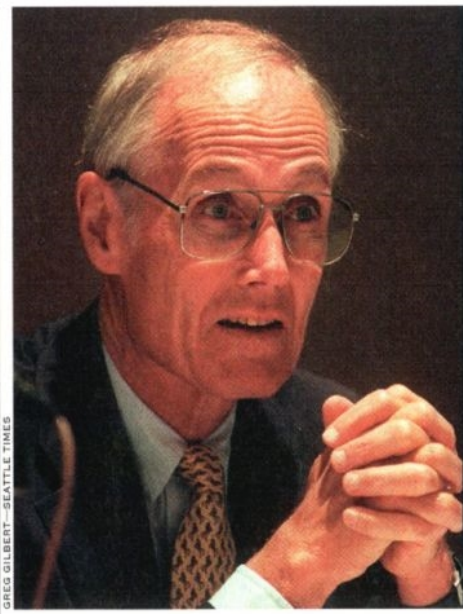
The next morning Lott made another important phone call, this one to Tom Daschle, the Senate's Democratic leader and the man serving as the White House's surrogate in negotiations over the structure of a trial. From his perch in Pascagoula, where he was juggling three phones and a fax machine while baby-sitting little Trent III, his seven-month-old grandson, Lott had been quietly collaborating with Daschle and other Senators on a plan to rush the impeachment issue through the Senate in just a few weeks. Daschle told Lott that the Democrats and the White House would go along with the idea, but Lott said he wasn't sure yet whether his fractious Republicans would do the same. The plan, which Lott would float publicly within hours, envisioned a sort of mini-trial, with opening arguments by prosecutors and the White House and few or no witnesses called by either side. After that would come a series of votes to determine whether the case against the President was strong enough to garner the 67 ayes, or two-thirds of the Senate, needed to remove Clinton from office. If, as Lott expected, the votes weren't there, the Senate would then consider a lesser punishment, such as censure. In an interview with TIME last week, Lott called the plan "a fair start" but conceded that "the situation is very fluid. It could be blown away by any number of people or events."

The explosions were nearly instantaneous. One Senate conservative, Oklahoma's James Inhofe, blasted Lott's gambit, telling reporters it was a "whitewash" designed to sacrifice the Constitution in the

name of expediency. The 13 House impeachment "managers" who will prosecute the case in the Senate were particularly aggrieved by Lott's scheme, complaining that he had not even bothered to consult them before it became public. Drawn from the ranks of the House Judiciary Committee and led by its chairman, Henry Hyde, the managers have been preparing for their star turns as prosecutors in the trial of the century. When Lott floated his plan, a manager griped, "It was like, 'Hey, what about us?'" In a stern three-page letter to Lott, Hyde bristled at the idea that their engagement might be a limited one. "We need not sacrifice substance and duty for speed," Hyde wrote.

The rocky start to the Senate phase of impeachment was a bad sign for the man who has more at stake than anyone—with the obvious exception of the President. Since he took over as majority leader from Bob Dole in mid-1996, Trent Lott, 57, has not lived up to the widely held expectation that he would assume the role of the G.O.P.'s pre-eminent national leader. More a pragmatist than an ideologue, and more interested in passing legislation than in delivering visionary speeches, Lott has preferred immersing himself in the mechanics of running the Senate to playing the role of party sovereign. As the impeachment saga played out in the House, Lott watched quietly from across Capitol Hill, praying it would never reach the Senate.

Now that it has, Lott has the chance to be the leader who brings the scandal to a dignified conclusion. But he's not particularly happy about the opportunity. Lott knows that no matter what he does, he'll be attacked—"bashed by the left," he told TIME, or "criticized by people on the right." But he also knows that the outcome—and how the process will be judged by both the public and history—depends largely on him. "I realize that there's plenty of room to handle it properly or improperly," he said. "And I'm going to try to work in a way that everybody feels like they had their fair shot."



GREG GILBERT—SEATTLE TIMES

THE STEALTH DEALMAKERS

The proposal Lott and Daschl are floating was first crafted by two Senators, Republican Slade Gorton of Washington, left, and Democrat Joseph Lieberman of Connecticut, who enjoy bipartisan respect and could be trusted to work quietly. Lieberman, an early critic of Clinton's behavior, wants a censure with some stinging language

That is the elegance in the Lott proposal. After the mini-trial, there would be two votes on whether to conduct a full-blown trial, each requiring a two-thirds vote to go ahead. In the probable event they would fail, the trial would adjourn and the Senate would take up censure. Temporarily setting aside the messy issue of how to craft a censure resolution that would satisfy all sides, the obsessively punctilious Lott had devised an exit strategy that seemed to have something in it for everyone. Conservatives would get a trial, albeit a brief one, and a chance to go on the record with a vote showing their desire to convict. Senate Democrats and moderate Republicans would get the promise of an abbreviated, dignified process and the option of voting to censure Clinton when it's over. The White House, meanwhile, would avoid the kind of lengthy regurgitation of the evidence that could cause a slow erosion of support among the dozen Senate Democrats who stand between Clinton and an early helicopter ride out of town.

But for Lott to succeed with his or any other plan, he'll have to placate not only Hyde and his fellow House prosecutors but also conservatives within his own caucus in the Senate. Suspicious that their leader is in the process of cutting an accommodating prefab deal—just as he did during last year's budget negotiations—some conservatives, like Inhofe, are already rebelling. To be done with the unpleasant duty of the trial, they claim, Lott is running roughshod over the Constitution and the rule of law, all in the service of rescuing the President. "Trent cannot be perceived as Bill Clin-

THE PRECOOKED DEAL

A mini-trial with something for everyone: few or no witnesses, test votes that show there's not enough support to convict Clinton; and the follow-up passage of a bipartisan censure. This is the proposal floated by Lott and Daschle.

Chance: 40%

THE SHORT CIRCUIT

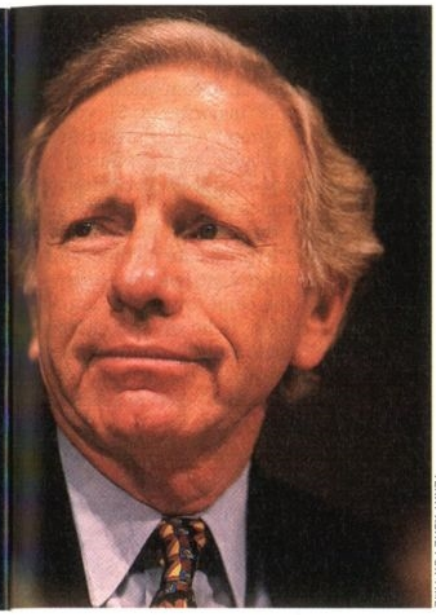
A trial is begun in mid-January and is halted soon thereafter, when 51 or more Senators vote in favor of a motion to dismiss, then approve a bipartisan measure censuring the President.

Chance: 25%

THE SCOT-FREE GETAWAY

A trial with limited witnesses that ends in an acquittal and is followed by a censure measure that fails because it is opposed by an unusual coalition of liberal Democrats, conservative Republicans and a few constitutional purists like Robert Byrd.

Chance: 15%



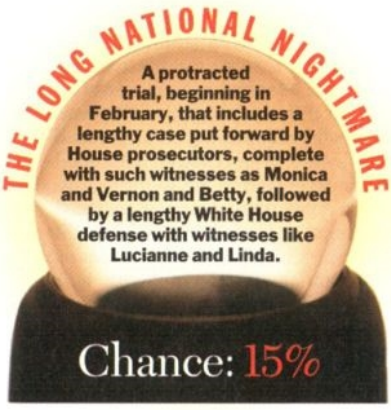
TERRY ASHE FOR TIME

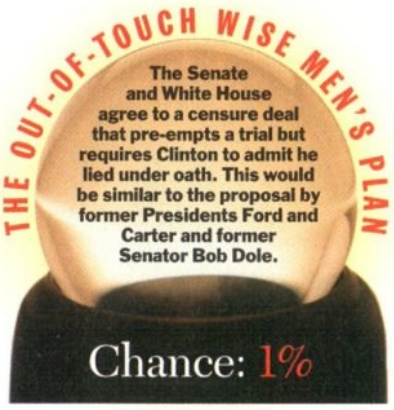
ton's savior," says a top G.O.P. leadership aide. "This is high stakes for Lott," says Sheila Burke, top aide to Bob Dole for years and now executive dean of Harvard's Kennedy School of Government. "Lott's dilemma is his right wing. They want a piece of flesh."

Another obstacle in Lott's way is his own propensity to blurt things out that he'd be better off keeping to himself—what a G.O.P. Senator described last week as "Trent's foot-in-mouth disease." It struck last summer, when Lott compared homosexuality to alcoholism and kleptomania, and again in mid-December, when he attacked the President's motives for launching air strikes on Iraq. Then it appeared one more time last week, when Lott went public with the outline of his plan for a streamlined impeachment trial without warning anyone on his staff, clearing it with any of his Senate colleagues or checking with House leaders. "This was not supposed to get out so early," complained a Senator close to the deal. But Lott acted impulsively. Stung by stories suggesting that he had taken refuge in Pascagoula while Washington was burning, the former head cheerleader from his days at Ole Miss wanted to set the record straight. "I wasn't hiding out," Lott explained. "I was working it."

In fact, Lott began thinking about ways he could avert a full-blown Senate trial in the days before the House voted to impeach Clinton on Dec. 19. "Trent has no interest in helping Bill Clinton," says a senior G.O.P. Senate official who knows Lott well. "But Trent wants to run the Senate. He doesn't want this thing screwing up the whole year." Lott also knew he couldn't scotch a trial entirely without enraging conservatives. So he went on television three weeks ago to insist that there would be a trial and "there won't be any dealmaking." But even as Lott spoke, one of his closest allies in the Senate, Washington's Slade Gorton, was quietly negotiating a deal with Joseph Lieberman, the Connecticut Democrat who had strongly criticized Clinton's behavior but who is advocating censure. Acting as surrogates for the Senate leaders, Gorton and Lieberman were the original authors of the plan for a mini-trial without witnesses. But Lott was deeply involved, calling Lieberman on several occasions as the plan came together.

For any deal aimed at shortening a trial to work, Lott knew he had to have the White House's tacit agreement not to call witnesses. He also needed assurances from Lieberman and Daschle that Clinton would not make a mockery of Lott's work by celebrating the Senate's turn to censure as a vindication of his behavior. In the wake of the House's partisan vote to impeach—and the polls showing the public siding overwhelmingly with Clinton—the early talk in the White House was more





K. COOPER—GAMMA LIAISON FOR TIME

Lott's Spot

From his Mississippi home, Lott spoke with TIME's *James Carney:*

■ On his negotiations with minority leader Tom Daschle:

Daschle and I have been talking regularly. We have tried to begin to shape a vision of how this would proceed, and we are consulting with a small group on both sides of the aisle. It is not written in stone. It is fluid. You've got to make sure that Senators on both sides are comfortable with it and feel like it's fair, that they know what we're talking about. You've got to make sure the House understands it and can live with the time frame we're talking about. This is not an effort to short-circuit it. It is an effort to have the evidence presented and have votes that bring this to a closure.

■ On whether to call witnesses:

If the House decides that there's some essential need for witnesses, we would have to honor that request within reason. Historically, witnesses have been called in impeachment trials. But I think that this is a different set of circumstances, where in fact they may not be necessary.

■ On whom he needs to answer to:

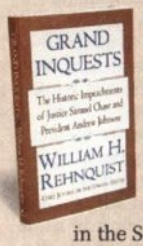
I've got three constituencies: Mississippi, the Senate and my conscience. I'm going to try to be true to all three. I always try to be statesmanlike. I don't always succeed in various people's minds. I realize this is a serious matter. I realize it's a constitutional matter. And I'm going to try to work in a way that everybody feels like they had their fair shot. And I may not vote for some of the things that I wind up setting up. But I'm going to do it as best I can, objectively and fairly, and the rest will be taken care of by my constituents and by history.

about combat than compromise. As a senior White House official put it, "There's a part of [Clinton's] mind that says a trial would be useful."

But at a meeting of the President's senior political advisers and lawyers last week, bravado gave way to pragmatism, and a decision was made to go along with the Lott plan. Better to end it quickly, the thinking went, while the White House could be sure that Republicans lacked the 67 votes to convict. Chief of staff John Podesta told Daschle that the White House was on board, but both sides agreed that it was important to play down any White House role in the deal for fear Republicans might reject it. "Right now, this is the Lott plan," said a senior Clinton aide. "He will eventually take pieces from everyone, but the whole game now is Lott." To help Lott quell his rebellion, the White House offered to make a tiny concession: Clinton lawyers will not dispute that the testimony taken by Starr is accurately reported—a move that might placate some G.O.P. Senators. But the President's team reserves the right to challenge the truth of that testimony as well as Starr's conclusions. That way, if the Lott plan collapses and a full-scale trial seems inevitable, the President's team won't have sacrificed its defense for the sake of a failed compromise.

By the time Chief Justice William Rehnquist administers the oath given to Senators before an impeachment trial, G.O.P. conservatives may have torpedoed Lott's plan. But as the majority leader is quick to point out, in the absence of an agreed-upon schedule, there is nothing to prevent a coalition of Democrats and moderate Republicans from putting together the simple majority of 51 votes needed to short-circuit a trial altogether and move immediately toward censure. His plan, Lott argues, at least gives House prosecutors a chance to make the case for conviction and then allows Senators to vote on whether to prosecute further. The question is whether Lott has the leadership skills and the clout to sell that argument to his critics. If he doesn't, Lott's legacy to the Senate and the country may be the dragging out of the scandal for many months to come. —***With reporting by Michael Duffy/Washington***

A Very Public Trial for a Very Private Justice



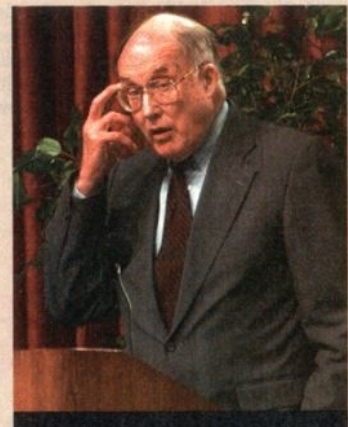
CHIEF JUSTICE WILLIAM REHNQUIST HAS THE kind of face that gets lost in a crowd, and that's the way he likes it. For years he has blocked broadcasting the work of the Supreme Court. But this week the professorial 74-year-old will cross the narrow street that separates his courthouse from the Capitol to become, at least for a while, the most televised person in America, the one in charge of President Clinton's trial in the Senate.

It's the role of a lifetime, and he's prepared. In 1992 he published *Grand Inquests*, a 278-page history of the 19th century impeachment trials of Justice Samuel Chase and President Andrew Johnson. The book is out of print, but frenzied demand from reporters and congressional staff members desperate for clues about how Rehnquist will run Clinton's trial drove it to No. 23 on *Amazon.com's* best-seller list and persuaded the publisher, William Morrow and Co., to reissue it next week in paperback. The book is painfully judicious in refusing to offer opinions but seems to applaud the acquittals of Chase and Johnson as victories for an independent judiciary and strong presidency.

Those who have watched his work at the Supreme Court over the past 27 years believe Rehnquist will be far more deferential than he is accustomed to being on his own turf. Rehnquist has been known to cut lawyers off in mid-sentence when their time has expired and to berate those who don't know or don't follow the rules. Lately he has also insisted somewhat grandly that lawyers call his colleagues on the Supreme Court "Mr. Justice" or "Madam Justice" rather than the more common "Judge."

In the Senate the rules may appear to give him great power—Senators are required to sit completely mute and put in writing any question they have for witnesses so he can read it aloud—but in fact he has no power to decide anything. Whatever rulings Rehnquist may make on questions of procedure and evidence can be overturned by majority vote: the jury is in charge of the judge.

When the proceedings start, his authority will depend largely on how impartial he appears. He is a celebrated conservative who as a law clerk to Supreme Court Justice Robert Jackson argued in a memo that segregated schools were constitutional. He wrote so many solo dissents in his early years as a Justice, when the court was more liberal, that he kept a Lone Ranger doll on his mantelpiece. Though he has hired some 80 law clerks, none has been black (he responds that he has "never excluded consideration of anyone" based on race). His natural ideological allies are the sort of Republicans who favor Clinton's conviction. But court watchers say he has moved toward the center over the years, partly due to the arrival of other conservatives who can hold down the right flank.


CHARLIE NEIBERGALL—AP

THE CHIEF JUSTICE'S book is being rushed back into print

Indeed, even liberals expect him to run the Senate trial in a way that commands bipartisan respect. "He's perfect for this job," says Stephen Gillers, a professor at New York University school of law. "He'll behave with all the politesse and decorum of a visitor in someone else's house. He has a keen sense of place." But if Rehnquist finds his unusual role less than appealing, he has himself partly to blame. When Clinton petitioned the court to defer the Paula Jones case until after his presidency, Rehnquist joined the other Justices in ruling that "it appears to us highly unlikely to occupy any substantial amount of petitioner's time"—proof that even the Chief Justice can make mistakes. —***By J.F.O. McAllister. With reporting by Andrea Sachs/New York***

The Olympics Turn into A Five-Ring Circus

Salt Lake City faces charges that it bought the games from the International Olympic Committee

By NADYA LABI

SALT LAKE CITY, AT THE base of the splendid and snowy Wasatch mountains, placed a close second to Nagano, Japan, in the race to host the 1998 Winter Olympics. So the pious and dogged capital of Utah went back to work on its fifth bid in three decades.

Ultimately, the International Olympic Committee awarded the city the 2002 Winter Olympics by an overwhelming margin. Mormon determination, it seemed, had paid off. Or had it?

After a leak to a Salt Lake City TV station by a disgruntled employee of the local organizing committee and provocative questions raised by a member of the I.O.C., the Salt Lake Olympic bidders stand suspected of bribing the I.O.C. members who decide where the next Olympics will take place. So far, four groups—the I.O.C., the U.S. Olympic Committee (whose probe is headed by former U.S. Senator George Mitchell), the Justice Department and a Utah ethics committee—have opened investigations into the mess. The IRS may be next.

I.O.C. membership has long been a sweet deal. Its 115 members don't get paid and now must refuse gifts valued in excess of $150. But they are among the most courted humans on the planet, allowed to accept first-class plane tickets, accommodations in five-star hotels and lavish dinners from bidding cities. Salt Lake City may have taken things a step further.

Between 1992 and 1998, the Salt Lake committee parceled out nearly $400,000 in scholarship money and other financial aid to 13 students. Conveniently, six of the recipients were related to I.O.C. members. Salt Lake committee tax reports, however, made no mention of the scholarships. A Utah health-care group donated $28,000 in services, including cosmetic eye surgery, to the I.O.C. cause. And the Salt Lake *Tribune* reported that the bid panel spent some $20,000 on guns and skis that presumably went to individuals associated with the I.O.C.

Far from heading for cover, some members of the local organizing committee are donning sackcloth and ashes. "Obviously, we did break the rules," says Ken Bullock, an abashed organizer. "The Games are an aphrodisiac. If you want something bad enough, you stretch the boundaries." He points out, however, that the pressure on a bidding city to be hospitable can be intense, and Salt Lake City was hardly the first to gild its welcome mat. "The I.O.C. allowed this sucking up," says Bullock.

The logic is a little shaky—just because someone is available to be bribed doesn't mean you bribe them—but the facts seem unassailable. I.O.C. executive Marc Hodler, a Swiss lawyer who has lately been acting as the organization's conscience, alleged last month that five to eight of his colleagues had solicited bribes from potential host cities. Hodler then accused the previous winning cities of Atlanta, Nagano and Sydney of corruption—a charge officials in all three cities deny. (A leader of Anchorage's bid effort revealed to the Denver *Post* that in 1992 and 1994 his committee had refused I.O.C. operatives seeking $30,000 in return for votes.)

Whether or not more wrongdoing is uncovered, the Games will go on—and they will almost certainly be held in Salt Lake City. Even with three years to go, the city is on a tight construction timetable, and it's not feasible to change the location. The 16-day extravaganza, expected to cost $1.5 billion, will be the most expensive Winter Games ever. Sponsors and broadcasters are expected to shoulder $1.1 billion of the cost, but Games promoters still have to raise $250 million from corporations. So far, none of the sponsors—among them Coca-Cola, IBM and SPORTS ILLUSTRATED (a Time Inc. magazine)—have indicated they will pull out, but the prospect worries local politicians. "If the Games don't break even," says Salt Lake councilwoman Deeda Seed, "we'll be handed a tax bill we can't afford." Already, US West has pointedly asked the Salt Lake committee if there will be more "surprises." The answer may be a long time coming; the Justice Department investigation into wire and tax fraud could take up to a year.

Meanwhile, the I.O.C. is scheduled to wrap up its internal review by Jan. 23. Members found to have solicited bribes may be forced to resign. A popular proposal, supported by the irrepressible 80-year-old Hodler, is that voting on host cities be limited to the executive board, which has 11 members.

There's no doubt that reform is needed. In September the Swiss senate granted the I.O.C. a tax abatement worth $1.5 million for "public service to Switzerland"—a country seeking the 2006 Winter Olympics for its mountain resort Sion. The lower house of parliament has yet to approve the windfall, but it may heed Finance Minister Kaspar Villiger, who persuaded reluctant senators to approve the tax break even if it meant "holding their noses."

So far, Sion is the front runner for the 20th Winter Olympics. —*Reported by Richard Woodbury/Salt Lake City, Melissa August/Washington and Robert Kroon/Geneva*

ILLUSTRATIONS BY JOE ZEFF

BAGHDAD BRIEFING

After riding out strikes, Saddam shoots back

HE KEPT HIS GUN HOLSTERED FOR A LITTLE more than a week after U.S. warplanes pounded his military sites, but now Saddam Hussein is firing back—and beginning the next round of his war with Washington. One of his mobile surface-to-air missile batteries near the northern town of Mosul launched three SAMs at U.S. jet fighters patrolling the no-fly zone last week. Two days later, more SAMs were launched from the Talil air base in southern Iraq against British and U.S. warplanes. Both times the pilots under attack jinked their planes in evasive maneuvers, avoiding the missiles. Then Air Force F-16 Falcons and Navy EA-6B Prowlers roared in with HARM antiradar missiles and precision-guided bombs to flatten the batteries.

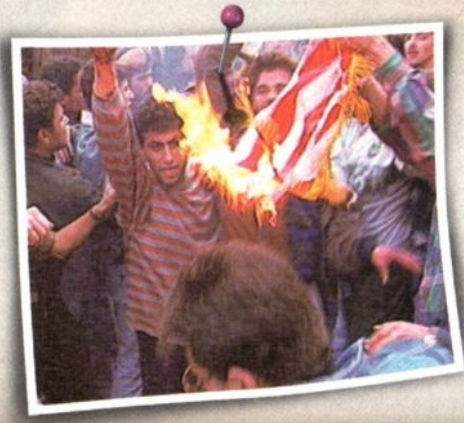
Iraqi Vice President Taha Yassin Ramadan vowed that Baghdad's "resistance will continue," and Washington believes him. By week's end Saddam had lobbed 11 SAMs at allied forces, and Air Force planes equipped to knock out SAM sites were rushed to the region in anticipation of more challenges to the no-fly zones. For now, the White House will respond to each provocation by counterattacking the offending battery. The Pentagon has no doubt what Saddam is up to. He hopes one of the SAMs will find its target and that a "golden BB will get him an American pilot," says a U.S. general. It would be a prized bargaining chip in the standoff, but even if Saddam fails, "defiance is still more important than success," says Georgetown University expert Amatzia Baram. After enduring four days of U.S. bombing, "Saddam needs to show his people he can bloody the American nose." —*By Douglas Waller/Washington*

CLOCKWISE FROM UPPER RIGHT: LOCKHEED MARTIN—AP; AFP; FALEH KHEIBER—REUTERS; NBC—UPI; AFP—DOD

TIME Map by Ed Gabel

BOMB-DAMAGE ASSESSMENT

THE PENTAGON SAYS its missiles and bombs hit 85 of 100 targets. Strikes on factories probably set back Saddam's missile program, but his chemical- and biological-weapons capability was left intact. Though warplanes nailed the barracks of the Special Republican Guards who protect Saddam, many were empty. "This is a wash," says arms expert Anthony Cordesman. "It's not a victory for Saddam, but it's definitely not a victory for the West."



THE NEIGHBORS

ANGRY DEMONSTRATORS took to the streets in Egypt, Jordan, Syria, Lebanon, Yemen, Morocco and the Palestinian territories after the four-day strike. Although Arab governments have been muted in their criticism, Arab parliamentarians meeting in Amman last week condemned the "unjust U.S.-U.K. aggression against Iraq." The apparent message: the U.S. can't count on staunch Arab support in a protracted battle with Saddam.

THE NO-FLY ZONES

DESPITE SADDAM'S PLEAS, the U.S. plans to continue its strict enforcement of the Iraqi no-fly zones. Saddam loathes the shackles. He sees them as an infringement of Iraqi sovereignty and a blow to his prestige. Tactically, the flight bans limit his control over rebellious Shi'ites in the south and Kurds in the north—a threat to his rule. Currently, U.S. planes patrol the zones every day, in all but the worst weather.

U.S. CONCERNS

FOR ALL THE FURY of Washington's December raids, the White House is still worried about keeping Saddam in check. There's little chance Iraq will take back the U.N. inspectors. The new U.S. plan: screw down economic sanctions and attack any renewed weapons development. But the CIA will have difficulty finding secret arms caches, and attacks may fracture coalition support for sanctions.

POLITICS OF SADDAM

DID THE U.S. CRUISE-AND-BRUISE strikes weaken Saddam's grip on power? The raids humiliated Saddam's generals, who were powerless to respond. That might prompt them to lash out against their leader—but it's an unlikely scenario. "And any bombing where he personally survives helps him," says a U.S. intelligence official. "It shows he can stand up to a superpower."

Desert Fox Scorecard

100	TARGETS
85	TARGETS HIT
415	CRUISE MISSILES LAUNCHED
600	BOMBS DROPPED
12	AVERAGE BOMBS AND MISSILES PER TARGET HIT
$750,000,000	COST OF BOMBS AND MISSILES

Sources: U.S. Department of Defense; Center for Strategic and International Studies

MEN WHO WOULD BE BIBI

Other Israeli politicians can't stand Netanyahu, but the voters may still stick by him

By **LISA BEYER** JERUSALEM

BENJAMIN NETANYAHU HAS FAILED. His fragile coalition—a pastiche of right-wing and centrist Israeli politicians—has been dashed by debate over the Palestinian peace process and riven by internal conflict. Halfway through his 4½-year term, Netanyahu has been forced to agree to new elections. All around him, Likud members of his coalition are defecting. The party's elder statesman, former Prime Minister Yitzhak Shamir, has called him "the angel of destruction." Hardly a voice has been raised in his defense.

Nevertheless, from all appearances, the Prime Minister of Israel is a happy fellow. Looking fresh and crisp in a blue suit, Netanyahu in an interview last week bounced on the edge of his seat like a man excited by a new challenge. "To the extent the elections will be about the issues, I will win," he said, and he seemed to believe it.

The coalition Netanyahu built after his 1996 election has been teetering for some time. Last January, Foreign Minister David Levy, fed up with what he felt was the Prime Minister's arrogance, quit, taking his five-member faction with him and trimming Netanyahu's majority in the Knesset to a single vote. And as the Prime Minister—following popular opinion and pressed by the Clinton Administration—negotiated an expansion of Palestinian self-rule in the West Bank, his ultra-right wing began to wobble. In November, when he withdrew troops from a chunk of the West Bank as part of the Wye accord, it rebelled.

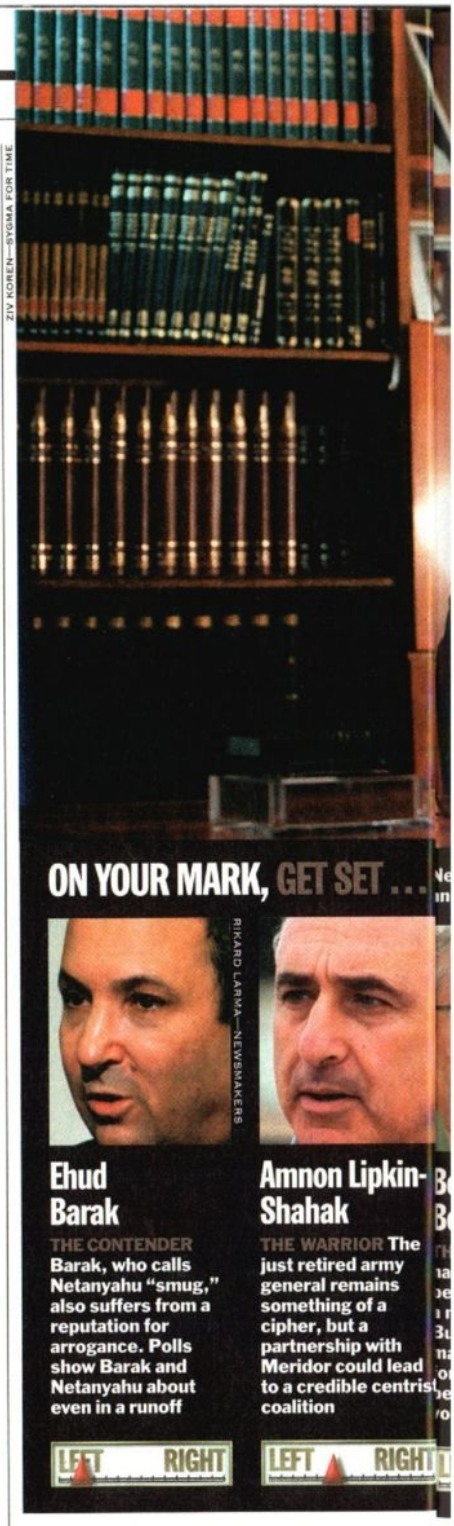
With the scent of political death upon him, Netanyahu, 49, has been showered with scorn by those challenging him for the leadership. From the left, Ehud Barak, leader of the opposition Labor Party, attacked him as a "smug, complacent man" who is "leading Israel to disaster." Blasts from within Likud were equally hot. Ex-Minister Ze'ev Benjamin Begin, the son of former Prime Minister Menachem Begin, accused Netanyahu of "capitulation" to the Palestinians. Another former Cabinet colleague, Dan Meridor, charged Netanyahu with making lying a norm. Within Israel and abroad, Netanyahu's enemies and allies alike charge that he habitually promises what they want from him—portfolios to politicians, peace deals to diplomats—and then reneges.

Among Netanyahu's challengers, Barak, 56, is the most serious. A former chief of staff, he is the Israeli military's most decorated soldier. But since entering civilian life four years ago, he has proved somewhat tone-deaf in politics. In March, for instance, he outraged Israelis by saying in a TV interview that if he were a young Palestinian, he'd probably join a terrorist organization. Still, recent polls show that he would run neck and neck with Netanyahu in the event of a runoff. Barak, eager for a boost, has hired James Carville, President Clinton's feisty political adviser. (Netanyahu has long employed Arthur Finkelstein, a right-wing American consultant.)

Barak's successor as army chief, Amnon Lipkin-Shahak, has added intrigue to the race with a so-far unofficial candidacy. Both men were protégés of slain Prime Minister Yitzhak Rabin. Lipkin-Shahak has joined with Meridor to form a centrist party; the two have agreed to let opinion polls dictate who gets the top slot on their ticket. Among the other contenders: Begin and possibly Ariel Sharon, currently Netanyahu's Foreign Minister but a man who has qualified his support for Netanyahu.

Elections are scheduled to take place May 17, with a runoff on June 1 if no candidate receives more than half the vote. Netanyahu expects his opponents to attack his credibility and trustworthiness, which aides acknowledge are his weak spots. Still, the profound mistrust that most of the chattering class has for Netanyahu may actually win him sympathy from disaffected immigrants, Orthodox Jews and blue-collar workers who resent the Establishment.

Netanyahu says he hopes to direct the campaign toward a single issue: Who is best suited to negotiate the final status of


ZIV KOREN—SYGMA FOR TIME

ON YOUR MARK, GET SET . . .

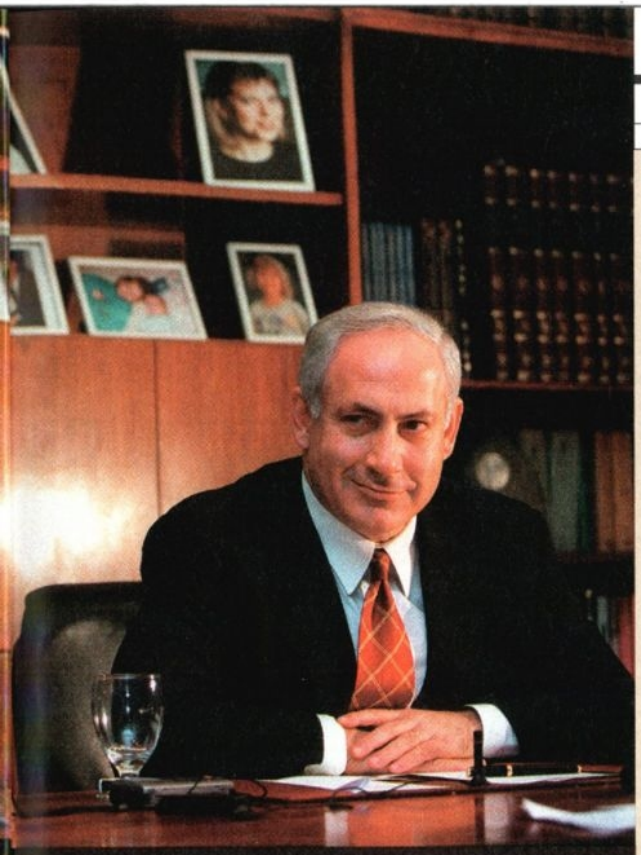
RIKARD LARMA—NEWSMAKERS

Ehud Barak

THE CONTENDER **Barak, who calls Netanyahu "smug," also suffers from a reputation for arrogance. Polls show Barak and Netanyahu about even in a runoff**

Amnon Lipkin-Shahak

THE WARRIOR **The just retired army general remains something of a cipher, but a partnership with Meridor could lead to a credible centrist coalition**



Netanyahu, poised and eager in his office last week, is facing a wide and furious opposition. Polls, however, still give him a good chance

NATI HARNIK—AP

Benjamin Begin

THE LEGACY **Begin has a golden pedigree—son of a national hero. But his rhetoric may be too much for Israel's peace-happy voters**

LEFT RIGHT

DAVID SILVERMAN—REUTERS (2)

Dan Meridor

OUT WITH THE OLD **National security expert Meridor left Likud to create a centrist party. Though widely respected, he does not yet have a significant base**

LEFT RIGHT

Ariel Sharon

HEAVYWEIGHT **The ex-general has a strong base among nervous rightists. He has hinted he might abandon Netanyahu, presumably if the incumbent starts to look doomed**

LEFT RIGHT

In Fighting Trim

In an exclusive interview, Netanyahu describes his fall—and his plan to return

■ **Do you regard the sudden call for elections as a failure?**

Well, it's a failure of the coalition. It was just a question of time before it fell because of a challenge from the right flank. I could have kept the government had I submitted to the terms posed to me from my right wing, which said that if I would tear up Oslo and the Wye accord they would stay. I refused, and equally I refused subsequent conditions from the left that said I [should] go ahead and implement Oslo regardless of Palestinian violations and no matter what violence the Palestinians perpetrate on us.

■ **What happens to the Wye agreement now?**

The Wye agreement is not suspended. It is awaiting Palestinian compliance. I wish Arafat would stop the violence, stop calling for the release of terrorist murderers, comply with the other promises the Palestinians made to us. If they would comply with their obligations and cease their violations, we would implement the next phase well before the elections.

■ **What would you do differently in a second term?**

I wouldn't do anything differently on the political side. Where I would do things differently is in the management of egos. I would say the Prime Minister has to devote equal time not only to the tasks of security and peacemaking and economic reform, all of which I did to my utmost, but to the maintenance, shall we say, of, ah, personal relationships.

■ **So you give yourself some of the blame for this?**

Oh, who doesn't make mistakes?

■ **Both major parties are being advised by American political consultants. To what effect?**

I don't think it has that much effect. It'll certainly make for a lively campaign. What I see imported from the U.S., I'm sorry to say, is the tactic of the lowest personal attack, which I believe in the end the voters will reject.

■ **Why is it that you're unpopular among politicians and popular with the people?**

It's the physics of the record disk. Those in the outer circle move with greater speed, and the closer you get to the pivot the slower they turn. So [*laughing*] it's the same thing. Those who are closest to the hub of politics move the slowest. It may take them a few years to accept the leadership. There's a cadre of people who were ahead of me when I entered the Likud, who never really accepted my leadership.

■ **The most common criticism of you across the political spectrum is that you are deceitful. Why?**

Every time somebody does not receive from you what they want, they say, "Netanyahu lied to me." That's another way of saying, "I didn't get from Netanyahu what I wanted."

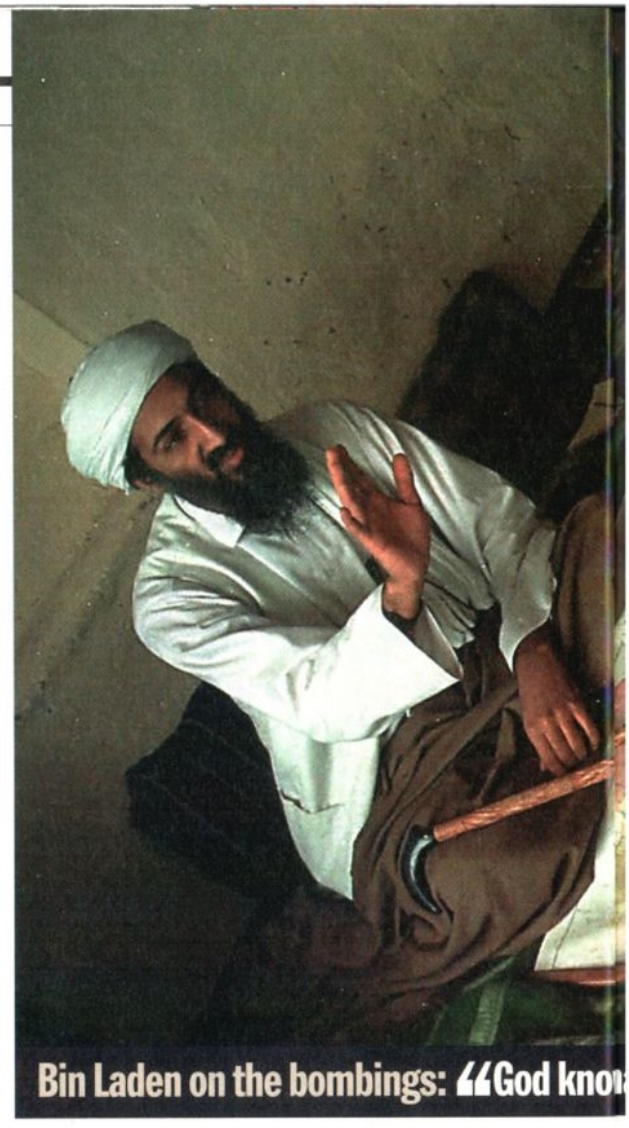
■ **Recently your father, of all people, suggested you might make a better Foreign Minister than Prime Minister.**

The addendum to that that you're not quoting is that [he said] nobody would be a better Prime Minister. I'll live with that. ■

the West Bank and Gaza Strip? He argues that the Wye accord proves he can make peace, and that it is better to have a right-winger bargain over the final pact than a leftist who will make a sucker deal. It's a powerful argument, Netanyahu knows, and one that keeps him in the running. ■

INTERVIEW

CONVERSATION WITH TERROR



Bin Laden on the bombings: "God kno

OSAMA BIN LADEN—THE ALLEGED MASTERMIND OF ATTACKS on two U.S. embassies—has been in hiding since the U.S. launched missiles against his bases in Afghanistan last August. Yet on Dec. 22, the summons suddenly came: Would Rahimullah Yusufzai, who reports for the *News* of Pakistan, as well as TIME and ABC, like to interview Bin Laden? After a car trip through the Afghan desert (and getting stuck in the sand three times), Yusufzai arrived at an encampment of three tents. Polite and given to praising God in nearly every sentence, Bin Laden sipped water from a cup (he was nursing a sore throat) and nestled an AK-47 as he spoke. Eager to deny reports that he has cancer, Bin Laden said he enjoys riding horses and playing soccer, but he used a stick to walk because of a bad back. He also spends time with his three wives and children in Afghanistan. Aides say his contact with the world is limited to newspaper and radio reports. Though he has a sat phone, it sits mostly idle: he fears the U.S. would use the signal to target an attack.

LETHAL LINKS

THE ORGANIZATION Al Qaeda, which has operatives around the world, is funded by Bin Laden's $100 million fortune

WHAT NEXT? The U.S. is demanding he face a murder trial, but the Taliban are likely to continue shielding him

TIME: *Are you responsible for the bomb attacks on the two American embassies in Africa?*

Osama bin Laden: The International Islamic Front for Jihad against the U.S. and Israel has, by the grace of God, issued a crystal-clear *fatwa* [decree] calling on the Islamic nation to carry on jihad [holy war] aimed at liberating holy sites. The nation of Muhammad has responded to this appeal. If the instigation for jihad against the Jews and the Americans in order to liberate al-Aksa Mosque and the Holy Ka'aba [Islamic shrines in Jerusalem and Saudi Arabia] is considered a crime, then let history be a witness that I am a criminal. Our job is to instigate and, by the grace of God, we did that, and certain people responded to this instigation.

TIME: *Do you know the men who have been arrested for these attacks?*

Osama bin Laden: What I know is that those who risked their lives to earn the pleasure of God are real men. They managed to rid the Islamic nation of disgrace. We hold them in the highest esteem.

TIME: *But all those arrested are said to have been associated with you.*

Osama bin Laden: Wadih el-Hage [an alleged Bin Laden associate who is being held in custody in New York City on charges stemming from the attacks on the embassies] was one of our brothers whom God was kind enough to steer to the path of relief work for Afghan refugees. I still remember him, though I have not seen him or heard from him for many years. He has nothing to do with the U.S. allegations. As for Mohamed Rashed al-'Owhali [another suspect in the bombings], we were informed that he is a Saudi from the province of Najd. The fact of the matter is that America, and in particular the CIA, wanted to cover up its failure in the aftermath of the events that took place in Riyadh, Nairobi, Dar es Salaam, Capetown, Kampala—and other places, God willing, in the future—by arresting any person who had participated in the Islamic jihad in Afghanistan. We pray to God to end the plight [of the arrested men], and we are confident they will be exonerated.

TIME: *How do you react to the December attack on Iraq by U.S. and British forces?*

Osama bin Laden: There is no doubt that the treacherous attack has confirmed that Britain and America are acting on behalf of Israel and the Jews, paving the way for the Jews to divide the Muslim world once again, enslave it and loot the rest of its wealth. A great part of the force that carried out the attack came from certain gulf countries that have lost their sovereignty. Now infidels walk everywhere on the land where Muhammad was born and where the Koran was revealed to him.

oiat we have been pleased at the killing of American soldiers."

The situation is serious. The rulers have become powerless. Muslims should carry out their obligations, since the rulers of the region have accepted the invasion of their countries. These countries belong to Islam and not the rulers.

TIME: *What can the U.S. expect from you now?*
Osama bin Laden: Any thief or criminal or robber who enters another country in order to steal should expect to be exposed to murder at any time. For the American forces to expect anything from me personally reflects a very narrow perception. Thousands of millions of Muslims are angry. The Americans should expect reactions from the Muslim world that are proportionate to the injustice they inflict.

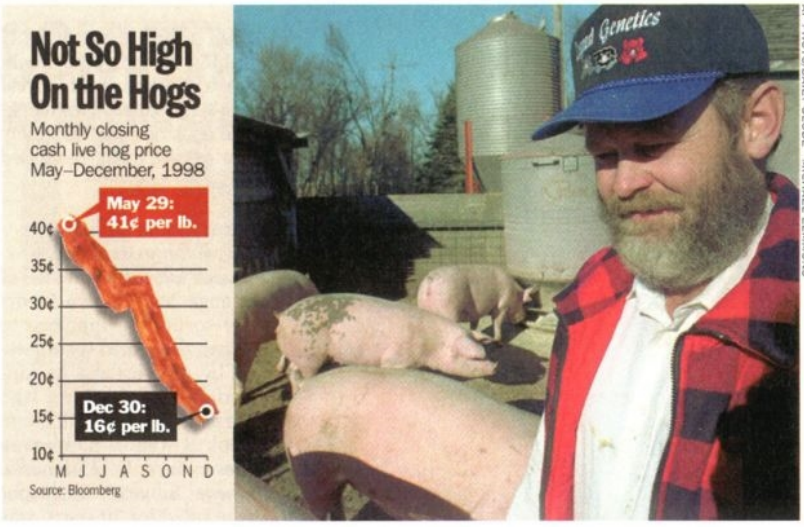
TIME: *The U.S. says you are trying to acquire chemical and nuclear weapons.*
Osama bin Laden: Acquiring weapons for the defense of Muslims is a religious duty. If I have indeed acquired these weapons, then I thank God for enabling me to do so. And if I seek to acquire these weapons, I am carrying out a duty. It would be a sin for Muslims not to try to possess the weapons that would prevent the infidels from inflicting harm on Muslims.

TIME: *The U.S. is trying to stop the flow of funds to your organization. Has it been able to do so?*
Osama bin Laden: The U.S. knows that I have attacked it, by the grace of God, for more than 10 years now. The U.S. alleges that I am fully responsible for the killing of its soldiers in Somalia. God knows that we have been pleased at the killing of American soldiers. This was achieved by the grace of God and the efforts of the *mujahedin* from among the Somali brothers and other Arab *mujahedin* who had been in Afghanistan before that. America has been trying ever since to tighten its economic blockade against us and to arrest me. It has failed. This blockade does not hurt us much. We expect to be rewarded by God.

TIME: *Is your Islamic message having an impact?*
Osama bin Laden: Winds of change have blown in order to lift the injustice to which the world is subjected by America and its supporters and the Jews who are collaborating with them. Look at what is happening these days in Indonesia, where Suharto, a despot who ruled for 30 years, was overthrown. The time will come, sooner rather than later, when criminal despots who betrayed God and his Prophet, and betrayed their trust and their nation, will face the same fate.

TIME: *But there are many Muslims who do not agree with your kind of violence.*
Osama bin Laden: We should fully understand our religion. Fighting is a part of our religion and our Shari'a [an Islamic legal code]. Those who love God and his Prophet and this religion cannot deny that. Whoever denies even a minor tenet of our religion commits the gravest sin in Islam. Those who sympathize with the infidels–such as the PLO in Palestine or the so-called Palestinian Authority–have been trying for tens of years to get back some of their rights. They laid down arms and abandoned what is called violence and tried peaceful bargaining. What did the Jews give them? They did not give them even 1% of their rights.

TIME: *America, the world's only superpower, has called you Public Enemy No. 1. Are you worried?*
Osama bin Laden: Hostility toward America is a religious duty, and we hope to be rewarded for it by God. To call us Enemy No. 1 or 2 does not hurt us. Osama bin Laden is confident that the Islamic nation will carry out its duty. I am confident that Muslims will be able to end the legend of the so-called superpower that is America. ■



AP PHOTO/DAILY GLOBE—MICHAEL LEMMONS

STUCK IN THE MUD: Midwest hog farmers like Gary Lonneman can't break even

Lean Times on the Farm

If hog prices are so low, why isn't pork cheaper? Struggling farmers want help—and some answers

By DANIEL EISENBERG

IT'S AN IRONY THAT MAKES GARY MULLER'S financial troubles that much harder to bear. If the Iowa hog farmer were to hang out at a local supermarket, he might suspect that his business was thriving as never before. After all, there's no lack of customers buying pork chops or roasts for dinner; and in spite of the Asian economic woes that devastated most American farmers in 1998, pork exports keep on growing. But while Americans pay top dollar for their hams or BLTs, Muller and the rest of America's 115,000 hog farmers may as well give their animals away (some are doing that). His 220-lb. pigs, which a little over a year ago fetched 60¢ per lb., now command around 15¢ per lb. When he's not selling his livestock at a loss, he's trying to rearrange his bank payments and save his century-old family farm from going under. "We're getting killed out here," he says.

The pigs, on the other hand, can't be killed fast enough—though 2 million a week are being butchered. And therein lies the problem. Hog farming, until recently the most profitable sector in agriculture, is stuck in the mud. A glut of live pigs on the market, exacerbated by a sudden drop in slaughterhouse capacity, has pushed the price of pigs down to levels not seen since the Depression. "It's a lethal mixture," says Al Tank, CEO of the National Pork Producers Council. Across the South and Midwest, farmers are losing thousands of dollars a day, drifting deeper into debt and near bankruptcy; fully 20% could be belly-up by spring. A government forecast on the hog supply last week promised little relief. "It's the most serious agricultural crisis in this century for an individual commodity," says Gilbert Hollis, a professor at the University of Illinois. The industry, which has lost $2 billion over the past 12 months, is asking the government for help.

On Christmas Eve, Washington answered the call. Secretary of Agriculture Dan Glickman increased federal purchases of pork for humanitarian aid, established a moratorium on direct loans for new production plants and urged supermarkets to start passing on savings to consumers and meat packers to buy at voluntary minimum prices (two in the Midwest have already started doing so).

Of course, at this point, no proposed remedy—including the idea of a "gilt lift" of 300,000 sows to hurricane-ravaged Central America—may do much for the independent hog farmer. George Bailey is one of that fading breed; he owns 650 sows in Walstonburg, N.C., and unlike corporate megafarms, isn't blessed with deep pockets. In the past year Bailey has had to use most of his savings just to stay afloat, and he still racked up $35,000 in additional debt. "We're slowly going broke," he notes. "The [meat] packers are making a killing."

Bailey isn't alone in his suspicions that something more than simple market forces is at play. Many farmers have pointed the finger at their Canadian brethren for flooding the market with swine, and are urging tougher import restrictions. Meanwhile, some critics believe that a few dominant corporate hog processors, like IBP or Smithfield, have unfairly profited from the farmers' misfortunes. "This isn't a matter of outmoded hog producers falling victim to the invisible hand of the market," says Senator Tom Harkin of Iowa. "Pork in the grocery store costs the same now as six months ago. An anticompetitive pork industry is victimizing farmers and consumers." Still, shoppers may begin to see savings at the butcher's counter in the next few months. Unfortunately, by then, hog farmers may not be able to bring home the bacon. —***Reported by Christopher Burbach/Omaha, Alison Jones/Durham and Dick Thompson/Washington***

Meanwhile, in the Citrus Aisle . . .

WHILE WAITING FOR A BREAK ON PORK PRICES, CONSUMERS can brace themselves for a jump in the cost of table oranges. The eight days of freezing weather that devastated California groves have already driven the wholesale price of the state's navel oranges to $25 a carton, up from $10 a few weeks ago. Shoppers can expect retailers to pass along that extra cost: prices could soar to $1.50 per lb., compared with 39¢ to 49¢ two weeks ago. Orange juice, however, should be unaffected. The juice crop comes from Florida and Brazil, which so far have enjoyed mild weather. "You can't compare oranges to oranges," says Kathy Jones, manager of futures research at Prudential Securities. Even table oranges may come down soon: a warming trend in California means that some of the crop might survive. In the meantime, drink your juice. ■

Lance Morrow

Is This Right? Who Has the Right to Say?

A mother of octuplets, one already gone, says God has blessed her

ONE BABY? FINE. TWINS? SURPRISE. TRIPLETS? HOW nice ... I think. Quadruplets? Gulp. Quintuplets? In the range of five babies and beyond, we enter a realm of fascinated horror, sublimated into sentimentality. We call the *Guinness Book of World Records* and the local TV news. If P.T. Barnum were here, we'd alert him; the circus loves biological anomalies, in the way that it cherishes those stunts in which eight clowns emerge from a Volkswagen.

But the intimate reality—what could be more intimate?—poses a sequence of haunting questions that ascend to the metaphysical. The womb is a very small apartment, and overcrowding creates the sort of triage dilemmas that doctors face on battlefields. Which one of the babies is one too many? The third? The fifth? The eighth? And since nature does not number the fetuses, how does one assign them priority in the event that "selective reduction" becomes the choice?

Months ago, doctors told Nkem Chukwu they couldn't be sure, but they thought she was probably carrying seven fetuses. She and her husband—devout Christians, Nigerian-born U.S. citizens—refused to abort any of them. "I wasn't even going to give it a second thought," she said last week as she was dismissed from St. Luke's Episcopal Hospital in Houston. God had blessed her, she explained, and she declared her babies "unique."

Unique they are. They required that their heroically stoical mother give up solid food and lie at an angle with her pelvis higher than her head for weeks in order to minimize pressure on the cervix.

When at last the babies, eight of them, were born, five days before Christmas and three months premature, they ranged in weight from 10.3 oz. to 1 lb. 10 oz., the world's first octuplets to be delivered alive. Within a week, the smallest baby, Odera, weighing hardly more than a small bird, died. As of the New Year, doctors, with disconcerting precision, gave the others a 92% chance of surviving.

Did Chukwu and her husband Iyke Louis Udobi make the right decision? And who has the authority to judge that decision? Baby boomers who have postponed parenthood 20 years or more increasingly turn to fertility drugs, knowing this will lead to twins 20% of the time and to triplets or more an additional 5% of the time. The sidewalks of Manhattan's Upper West Side are clogged these days by strollers for twins and triplets, pushed by gray-haired parents. And it's no longer unusual in any part of the country to meet women in their mid-40s who are pregnant for the first time.

But before you arrive at the metaphysical questions, you face the medical ones. Chukwu, who miscarried triplets earlier in 1998, was treated this time with injectable fertility drugs called gonadotropins at a Houston clinic. Such drugs stimulate the follicles to mature in preparation to release eggs. The woman is monitored, and if a large number of follicles mature, most doctors advise her to cancel the cycle in order to avoid multiple births. Canceling the cycle is simple; either by withholding a second drug that stimulates the follicles to release eggs or, if the eggs are released anyway, by avoiding sexual relations for a while.

ADREES A. LATIF—REUTERS

GOING HOME: Mom and Dad leave the hospital

Nkem Chukwu, who miscarried triplets earlier in 1998, was being treated with injectable fertility drugs called gonadotropins

It isn't clear why Chukwu did not take such steps early on. Doctors say many patients have invested so much time, effort and money—$10,000 or more for in vitro fertilization, lesser amounts for fertility drugs—that it's difficult to persuade them to end a cycle.

Multiple births have multiple costs. They take a "terrible toll" on a woman's body, says Dr. Thomas Vaughn, a fertility expert in Austin. "A human uterus is made to carry 6 to 8 lbs. Beyond that, women have trouble walking, breathing; it's hard on the heart." The babies are punished as well; many multiple-birth preemies suffer brain damage and other problems. Finally, there is another cost: the hospital bill for *each* of Chukwu's surviving babies will be $250,000, and that's just the start.

We thrash out the ethics of these matters in a sort of MSNBC of the mind, a noisy internal theater, entertaining first one dogmatic view and then its opposite. Is "selective reduction" moral? Are fertility drugs a blessing or a contravention of nature's or God's decision?

I knew a brilliant man, of my father's generation, who, when drunk, would recount the horrors of his days as a Marine on Guadalcanal. There he glimpsed "the madness of God" in nature's orgies of simultaneous life and death, generation and decay. Surely a similar dissonance hums now in all of our medical ingenuities. Fertilizations run amuck, while the dying plead to be disconnected from life support.

Thus, hyperfertility becomes another part of surreal life as the millennium ends here on Planet Kevorkian. All life is sacred. But as these manipulations (to generate life, to cancel it) go on, I think I hear the distant, rushing sound of divinity escaping.

—Reported by Hilary Hylton/Austin

The Biotec

By WALTER ISAACSON

RING FAREWELL TO THE CENTURY OF PHYSICS, THE ONE IN WHICH WE SPLIT THE ATOM and turned silicon into computing power. It's time to ring in the century of biotechnology. Just as the discovery of the electron in 1897 was a seminal event for the 20th century, the seeds for the 21st century were spawned in 1953, when James Watson blurted out to Francis Crick how four nucleic acids could pair to form the self-copying code of a DNA molecule. Now we're just a few years away from one of the most important breakthroughs of all time: deciphering the human genome, the 100,000 genes encoded by 3 billion chemical pairs in our DNA.

Before this century, medicine consisted mainly of amputation saws, morphine and crude remedies that were about as effective as bloodletting. The flu epidemic of 1918 killed as many people (more than 20 million) in just a few months as were killed in four years of World War I. Since then, antibiotics and vaccines have allowed us to vanquish entire classes of diseases. As a result, life expectancy in the U.S. jumped from about 47 years at the beginning of the century to 76 now.

But 20th century medicine did little to increase the natural life-span of healthy humans. The next medical revolution will change that, because genetic engineering has the potential to conquer cancer, grow new blood vessels in the heart, block the growth of blood vessels in tumors, create new organs from stem cells and perhaps even reset the primeval genetic coding that causes cells to age.

Our children may be able (I hope, I fear) to choose their kids' traits: to select their gender and eye color; perhaps to tinker with their IQs, personalities and athletic abilities. They could clone themselves, or one of their kids, or a celebrity they admire, or maybe even us after we've died.

h Century

In the 5 million years since we hominids separated from apes, our DNA has evolved less than 2%. But in the next century we'll be able to alter our DNA radically, encoding our visions and vanities while concocting new life-forms. When Dr. Frankenstein made his monster, he wrestled with the moral issue of whether he should allow it to reproduce: "Had I the right, for my own benefit, to inflict the curse upon everlasting generations?" Will such questions require us to develop new moral philosophies?

Probably not. Instead, we'll reach again for a time-tested moral notion, one sometimes called the Golden Rule and which Immanuel Kant, the millennium's most meticulous moralist, gussied up into a categorical imperative: Do unto others as you would have them do unto you; treat each person as an individual rather than as a means to some end.

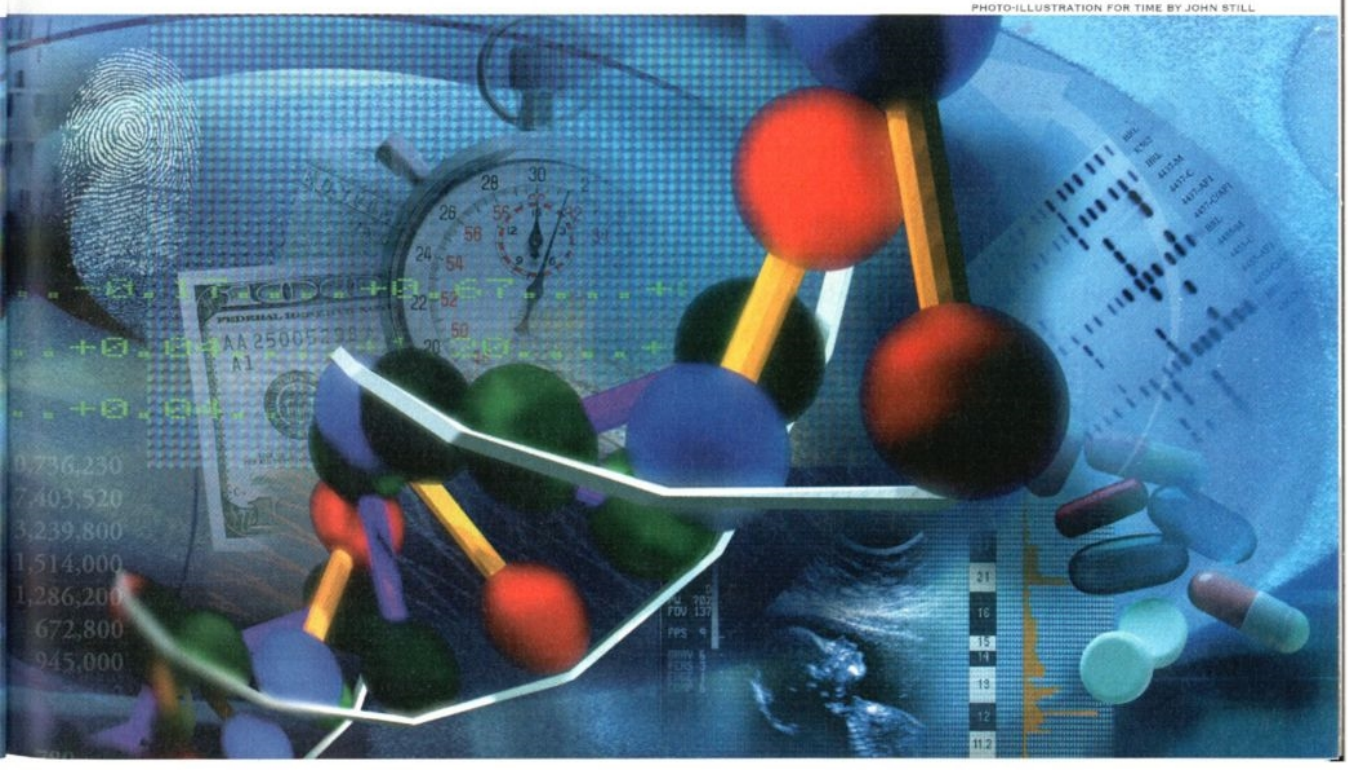
Under this moral precept we should recoil at human cloning, because it inevitably entails using humans as means to other humans' ends—valuing them as copies of others we loved or as collections of body parts, not as individuals in their own right. We should also draw a line, however fuzzy, that would permit using genetic engineering to cure diseases and disabilities (cystic fibrosis, muscular dystrophy) but not to change the personal attributes that make someone an individual (IQ, physical appearance, gender and sexuality).

The biotech age will also give us more reason to guard our personal privacy. Aldous Huxley, in *Brave New World*, got it wrong: rather than centralizing power in the hands of the state, DNA technology has empowered individuals and families. But the state will have an important role, making sure that no one, including insurance companies, can look at our genetic data without our permission or use it to discriminate against us.

Then we can get ready for the breakthrough that could come at the end of the next century and is comparable to mapping our genes: mapping the 10 billion or more neurons of our brain. With that information we might someday be able to create artificial intelligences that think and experience consciousness in ways that are indistinguishable from a human brain. Eventually we might be able to replicate our own minds in a machine, so that we could live on without the "wetware" of a biological brain and body. The 20th century's revolution in infotechnology will thereby merge with the 21st century's revolution in biotechnology.

But this is science fiction. Let's turn the page now and get back to real science. ■

PHOTO-ILLUSTRATION FOR TIME BY JOHN STILL



Competition from private labs has forced the Human Genome Project into a frantic rush to finish first

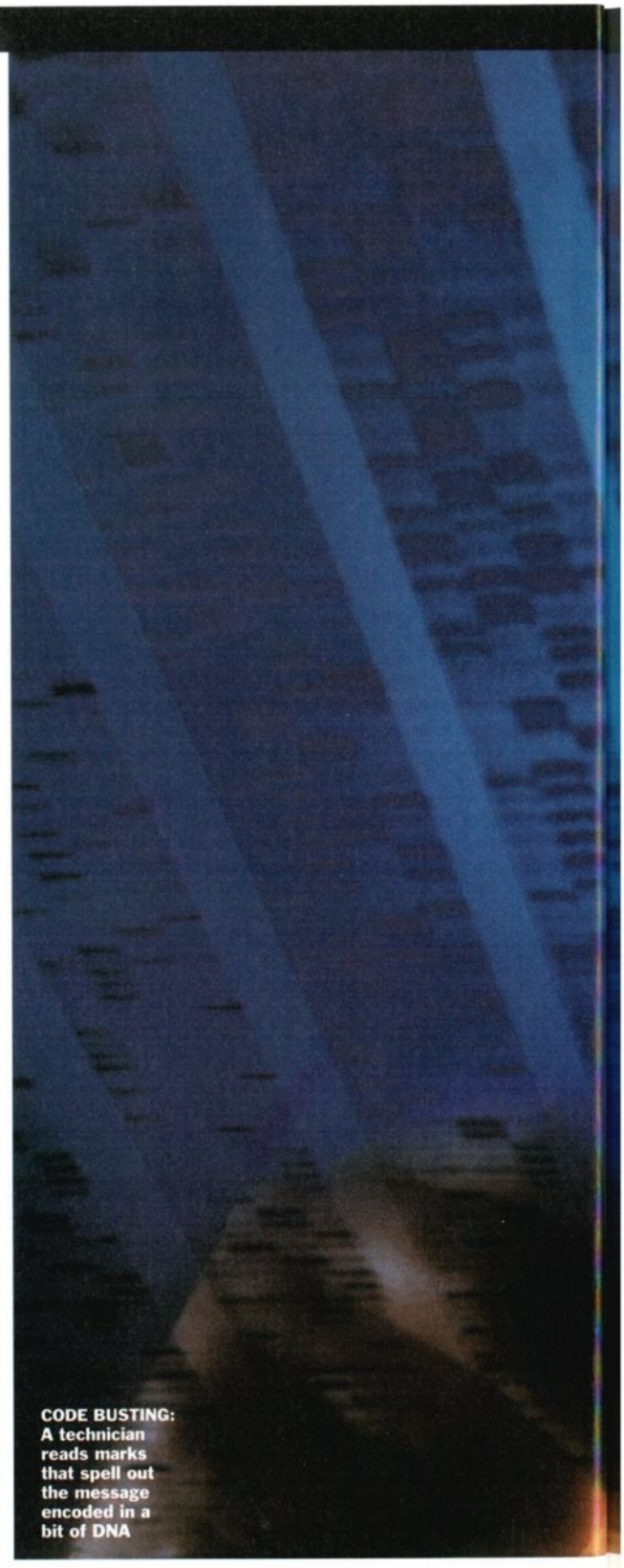
Racing To Map Our DNA

By MICHAEL D. LEMONICK and DICK THOMPSON

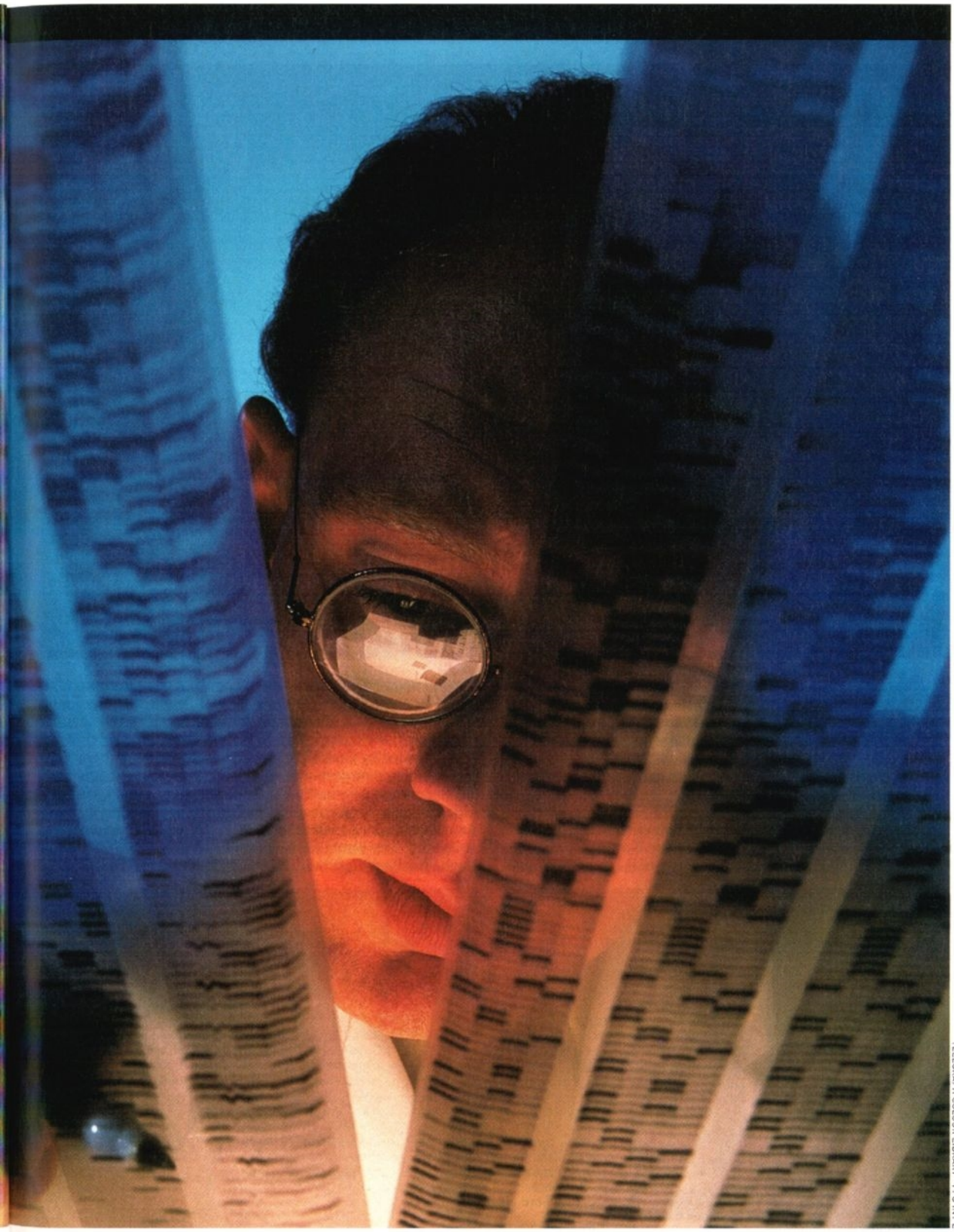
WHEN THE HUMAN GENOME PROJECT was launched a little under a decade ago, boosters compared it with the Manhattan Project or the mission to put men on the moon: an effort so complex and so broad in scope that only the government had the financial and bureaucratic resources to pull it off—yet with such huge potential payoffs that virtually no resources should be spared.

By the time the project was complete, promised its advocates, science would at last have access to the "book of life"—the precise biochemical code for each of the 100,000 or so genes that largely determine every physical characteristic in the human body. Once researchers knew that, they'd be able to figure out exactly how each gene functions—and, more important, malfunctions to trigger deadly illnesses from heart disease to cancer.

Important as it was, the job would take some time. Unlike the atom bomb or the space race, there was no Hitler or Khrushchev who threatened to get there first. Without such external dangers forcing them to pull out all the stops, federally funded genome-project scientists figured they could move at their own pace; they would finish up in 2005 or thereabouts.



CODE BUSTING: A technician reads marks that spell out the message encoded in a bit of DNA



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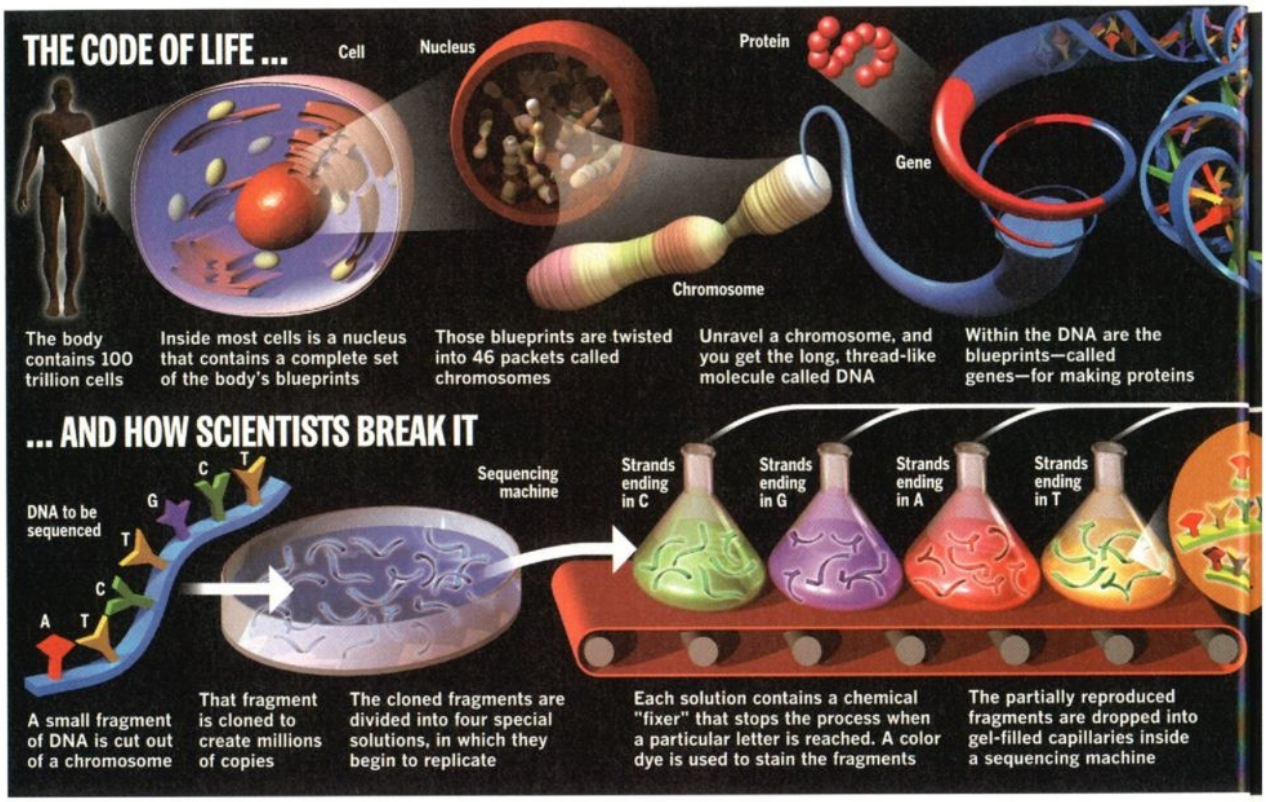


They figured wrong. The Nazis and the communists may be history, but an even more electrifying force has arisen to put the fear of God into the genome project: the profit motive. Pharmaceutical companies stand to make incalculable billions of dollars by turning genome research into new treatments for a dizzying array of diseases. And the companies that manage to get the information first—and lock up what they find with patents—will profit most (*see box*).

It's no surprise, therefore, that private firms have plunged into human-genome projects of their own. Nor is it surprising, given the potential payoff, that their scientists have found ways to speed up the decoding process. Indeed, one such company—Celera Genomics Corp., led by maverick scientist Craig Venter (*see following story*)—declared last spring that it would have the job substantially wrapped up in three years.

Blindsided by Venter's surprise announcement, leaders of the federal genome project—which is being carried out at university and government labs in the U.S., at the Sanger Centre near Cambridge, England, and at facilities in Germany and Japan—spent the summer rethinking their schedule. The result: an announcement last fall that they would finish up by 2003 rather than 2005, with a rough "working draft" of the genome to be published by 2001.

From Mendel To Monica

1866 Austrian botanist and monk Gregor Mendel proposes basic laws of heredity based on cross-breeding experiments with pea plants. His findings, published in a local natural-history journal, are largely ignored for more than 30 years.


CORBIS-BETTMANN

1882 While examining salamander larvae under a microscope, German embryologist Walther Fleming spots tiny threads within the cells' nuclei that appear to be dividing. The threads will later turn out to be chromosomes.

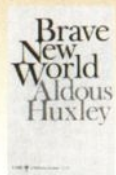
1883 Francis Galton, a cousin of Charles Darwin's and an advocate of improving the human race by means of selective breeding, coins the word eugenics.

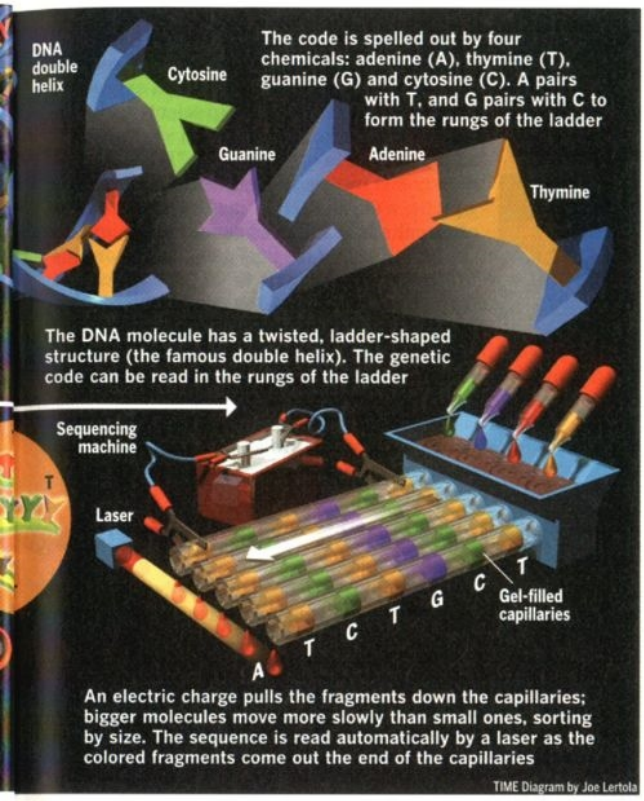

GRANGER COLLECTION

1910 U.S. biologist Thomas Hunt Morgan's experiments with fruit flies reveal that some genetically determined traits are sex linked. His work also confirms that the genes determining these traits reside on chromosomes.

1926 U.S. biologist Hermann Muller discovers that X rays can cause genetic mutations in fruit flies.

1932 Publication of Aldous Huxley's novel *Brave New World*, which presents a dystopian view of genetic engineering.





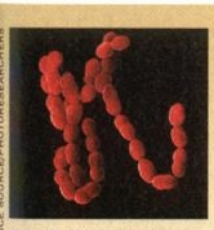
The measured march to decode the human genome, in short, has turned into a headlong horse race—and the rivalry isn't always polite. The federal genome project, critics carp privately, has been shockingly mismanaged and is sorely lacking in vision. Private efforts, counter some in the public project, are pirate operations that seek to lock critical segments of God's genomic handiwork behind a barricade of patents. Beyond that, they say, speeding up the pace of discovery could lead to slapdash, incomplete results. "If this is the book of life," sniffs Francis Collins, director of the National Human Genome Research Institute, in Bethesda, Md., and one of the leaders of the federal Human Genome Project, "we should not be satisfied with a lot of mistakes or holes."

Completeness and accuracy were the Human Genome Project's twin mantras from its formal start in 1990. At that point, researchers had already painstakingly identified more than 4,000 of the 100,000 genes that serve as the blueprint for a functioning human being—each gene carrying instructions that tell cells how to produce a specific protein. Scientists had located about 1,500 genes, in a rough way, on the 46 chromosomes—the long, twisted strands of DNA cradled in protein at the heart of every human cell. But they had deciphered, or sequenced, only a handful of the many-hundred-word "sentences" that each gene represents—sentences made up of three-letter "words" built in turn from four available molecular "letters," represented by *A, T, C* and *G*.

THE PROJECT'S $3 BILLION MANDATE: SEQUENCE THE entire 3 billion-letter human genome with high precision as a prelude to figuring out eventually what protein each gene produces and for what purpose (*see diagram*). The process can be likened to mapping out a route from San Francisco to New York City by walking the entire distance and noting every hill and valley along the way. It's slow but precise. After eight years, some 7% of the human genome has been sequenced in encyclopedic detail.

But while the genome project has been methodically chronicling the details of human cells—including long stretches of DNA, amounting to some 97% of the total, that contain no genes at all—private companies have opted for a very different approach. Their maps are more like satellite photographs that take in the entire route but concentrate only on the highlights. "The thing people are highly interested in," says Randal Scott, president and chief scientific officer at Incyte Pharmaceuticals, based in Palo Alto, Calif., one of the players in the private-sector gene-mapping game, "is where all the cities are. You don't need to document all the trees and gullies and ditches." Once those landmarks are identified, scientists assume, they can focus on them in greater detail.

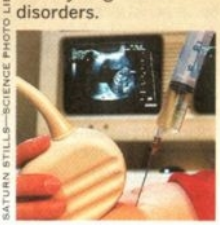
Scott's rivals at Genset, based in France, are taking a similar approach: their map, to be completed in early 2000, will highlight just 60,000 of some 10 million biochemical "beacons" found along the human genome. By comparing the DNA of many individuals in and around these signposts, Genset hopes to pick out specific genes whose malfunctions actually cause disease. It has already begun to work. Using this technique, says Genset chief genomics officer Dr. Daniel Cohen, the company has found two different genes involved in prostate cancer. Cohen points out that the 20 most common diseases, which kill about 80% of the population, are



HANK MORGAN—SCIENCE SOURCE/PHOTORESEARCHERS

1944 Working with pneumococcus bacteria, Oswald Avery, Colin MacLeod and Maclyn McCarty prove that DNA, not protein, is the hereditary material in most living organisms.

1950 British physician Douglas Bevis describes how amniocentesis can be used to test fetuses for Rh-factor incompatibility. The prenatal test will later be used to screen for a battery of genetic disorders.



SATURN STILLS—SCIENCE PHOTO LIBRARY/PHOTORESEARCHERS

UPI/CORBIS-BETTMANN

1953 American biochemist James Watson and British biophysicist Francis Crick announce their discovery of the double-helix structure of DNA, the molecule that carries the genetic code.

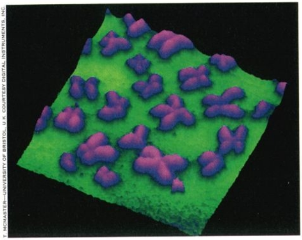
1964 Stanford geneticist Charles Yanofsky and colleagues prove that the sequence of nucleotides in DNA corresponds exactly to the sequence of amino acids in proteins.

1969 A Harvard Medical School team isolates the first gene: a snippet of bacterial DNA that plays a role in the metabolism of sugar.

1970 University of Wisconsin researchers synthesize a gene from scratch.

1973 American biochemists Stanley Cohen and Herbert Boyer insert a gene from an African clawed toad into bacterial DNA, where it begins to work. Their experiment marks the beginning of genetic engineering.

KEN M. HIGHFILL—PHOTORESEARCHERS



T. MCMASTER—UNIVERSITY OF BRISTOL, U.K. COURTESY DIGITAL INSTRUMENTS, INC.

GENE PACKETS **Chromosomes, purple, dot the molecular landscape in this image from an atomic-force microscope**

ed gene sequencer he'd acquired for his lab.

Decoded cDNA began tumbling out of his machine. A portion of these decoded regions were used as tags—he called them expressed sequence tags (ESTs)—to help scientists distinguish one gene from another and identify related genes even in other species. "His invention of ESTs was inspired," says Victor McKusick, a geneticist at Johns Hopkins University who is often called the father of genetic medicine. In June 1991, when Venter published his first paper based on this work, scientists had identified only about 4,000 genes, each one representing years of painstaking labor. In one day, Venter added 347 new genes to the list. Soon he was finding 25 a day.

Officials at the National Institutes of Health were delighted that one of their own had struck the mother lode, and they rushed to patent Venter's genes. But across the NIH campus, James Watson, who had won a Nobel for his co-discovery of the structure of DNA and who was then running NIH's Human Genome Project, was outraged. This wasn't science, he insisted. "Virtually any monkey" could do that work, Watson fumed in the opening salvo of a battle that would rage for months—and which smolders to this day. To patent such abbreviated genetic material, said Watson, was "sheer lunacy" that would entangle genetic research in legal issues and slow it to a crawl. When the battle was over, the NIH had withdrawn the patent proposal and Watson was no longer head of the genome project. Gone too were Venter and his wife and collaborator, Claire Fraser.

Freed from the confines of the NIH, Venter took an offer from a venture capitalist to head his own research facility, which he named The Institute for Genomic Research—TIGR, or "tiger." The private sector gave him the resources to find genes as fast as he could.

But in 1994 Johns Hopkins

Critics privately carp that the federal genome project has been shockingly mismanaged

probably linked to some 200 genes out of the body's 100,000. It only makes sense, he says, to look first at those genes.

As narrowly focused as their efforts are, Cohen and Scott are using gene-mapping techniques that are not very different from the Human Genome Project's. Craig Venter, on the other hand, has taken a radical approach, one that resembles paper shredding more than it does mapmaking.

Venter's reputation as a creative thinker was made back in the late 1980s. He was studying genes at the National Institutes of Health when he came to a humbling realization: while the greatest minds in biochemistry still hadn't figured out how to locate a gene efficiently, cells do it all the time. Cells, moreover, tap into only those genes they need and ignore the rest.

That was fine with Venter, since the strips of DNA that are actually being used as blueprints for constructing a protein are where the action is. So Venter decided to concentrate on these active parts. He focused on the so-called messenger RNA, or mRNA, which ferries instructions from DNA over to the cell's protein-making machinery. This is the essence of the gene, and it was these stripped-down genetic instructions—copied into a more stable form known as cDNA—that he fed into an automat-

WHAT PEOPLE THINK

Should insurance companies have access to your genetic record or DNA without permission?

Yes 6% No 94%

Should employers be able to obtain access to employees' genetic records or DNA without permission?

Yes 5% No 95%

*From a telephone poll of 1,031 adult Americans taken for TIME/CNN last month by Yankelovich Partners Inc. Margin of error ±3%. "Not sures" omitted.

1975 Scientists at an international meeting in Asilomar, Calif., call for guidelines for recombinant-DNA research.

1976 The first genetic-engineering company, Genentech, is founded in South San Francisco.

JIM COLLISON

1978 Scientists from Genentech and a Duarte, Calif., medical center clone the gene for human insulin.

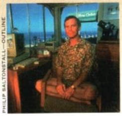
1980 Researchers successfully introduce a human gene—one that codes for the protein interferon—into a bacterium.

1980 Martin Cline and co-workers create a transgenic mouse, transferring functional genes from one animal into another.

1982 The U.S. Food and Drug Administration approves the first genetically engineered drug, a form of human insulin produced by bacteria.

1983 Researchers locate a genetic marker for Huntington's disease on chromosome 4. Their achievement leads to a screening test, but the disorder remains incurable. The gene itself will be found 10 years later.

1983 While driving along a California highway, Kary Mullis, a biochemist at Cetus Corp., conceives of the so-called polymerase chain reaction, or PCR, a technique that will enable scientists to rapidly reproduce tiny snippets of DNA.



PHILIP SALTONSTALL—OUTLINE

Nobelist Hamilton Smith challenged Venter to do more. At the time, Venter was using a technique called shotgunning. In essence, shotgunning amounts to putting DNA into a chemical Cuisinart. High-frequency sound waves shred the long stringy molecule into tiny fragments. The fragments are cloned in bacteria, and then, following what has become standard gene-mapping procedure, the bugs are ripped open and their DNA is run through a gene-sequencing machine.

But because the original DNA has been torn into so many random bits of genetic gibberish (as opposed to the predictable fragments made by gene-cutting enzymes), scientists need powerful computers to determine where the tiny fragments overlap. This is tough enough when you're sequencing a small part of a chromosome. But now Smith urged Venter to try it out, not merely on a strip of DNA

VOLKER STEGER—SCIENCE LIBRARY/PHOTORESEARCHERS

TEST-READY
This gel strip contains DNA fragments that have been separated by electric charge for sequencing

eand is sorely lacking in vision

but on an entire genome. He proposed *Haemophilus influenzae*, a bacterium that causes ear infections and meningitis. Until then, only a few small viruses, whose genomes had tens of thousands of genetic letters, had been entirely decoded. *H. flu* had 1.8 million.

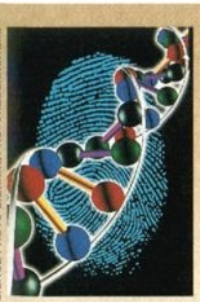
The audacious proposal was quickly denied federal funding. Venter and Smith pushed ahead anyway—and within a year they had succeeded. The publication of their 1995 paper in *Science* was a landmark that galvanized researchers. For the first time, the genetic secrets of an entire living organism had been exposed.

Today, four years later, a total of 20 genomes have been fully decoded, 10 of them at TIGR. In December scientists at Washington University in St. Louis, Mo., and at the Sanger Centre passed a new milestone by decoding the first animal genome, that of a tiny roundworm, *Caenorhabditis elegans*. At 97 million letters, *C. elegans'* genome is by far the most sophisticated ever sequenced. But if Venter's newly formed Celera (derived from the word celerity, which means swiftness) can pull it off, his proposal to shotgun the entire 3 billion-letter human genome in three years will make the roundworm's DNA look downright puny.

Venter admits that whole-genome shotgunning will leave gaps in the sequence where segments can't be fitted perfectly. But as he points out, traditional sequencing leaves holes as well. Like the government's gaps, his can be filled in later—and fast. "Let's say there are 50,000 holes averaging 83 letters each," he says. "At the rate we plan to clone and sequence DNA, we could close those in a day."

But many scientists believe that Venter won't be able to complete the genome-reassembly process. They liken the job to taking a year's worth of issues of a magazine like this one, chopping the pages into one-line fragments, then trying to put the fragments back together without a single typo. As daunting as that seems, imagine that up to 30% of the text consists of nearly identical strings of words up to 7,000 letters long. Assembling these "repeat sequences," says the genome project's Francis Collins, is "a challenge to anyone who doesn't break it down into bite-size pieces."

Whether or not Venter succeeds in putting his Humpty Dumpty genome back together again, his basic premise, shared by the competition at Genset and Incyte, remains compelling: you don't need the entire genome mapped to high precision to make



ALFRED PASIEKA—SCIENCE PHOTO LIBRARY/PHOTORESEARCHERS

1984 Alec Jeffreys, of Britain's University of Leicester, develops "genetic fingerprinting," which uses unique sequences of DNA to identify individuals.

1985 First use of genetic fingerprinting in a criminal investigation.

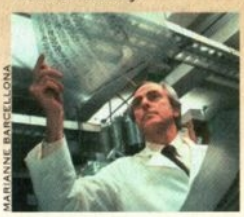
1986 The FDA approves the first genetically engineered vaccine for humans, for hepatitis B.

1988 Harvard University is awarded the first patent for a genetically altered animal, a mouse that is highly susceptible to breast cancer.

1989 Creation of the National Center for Human Genome Research, headed by James Watson, which will oversee the $3 billion U.S. effort to map and sequence all human DNA by 2005.

1990 Formal launch of the international Human Genome Project.

1990 American geneticist W. French Anderson performs the first gene therapy on a four-year-old girl with an immune-system disorder called ADA deficiency.



MARIANNE BARCELLONA

1990 Publication of Michael Crichton's novel *Jurassic Park*, in which bioengineered dinosaurs roam a paleontological theme park; the experiment goes awry, with deadly results.

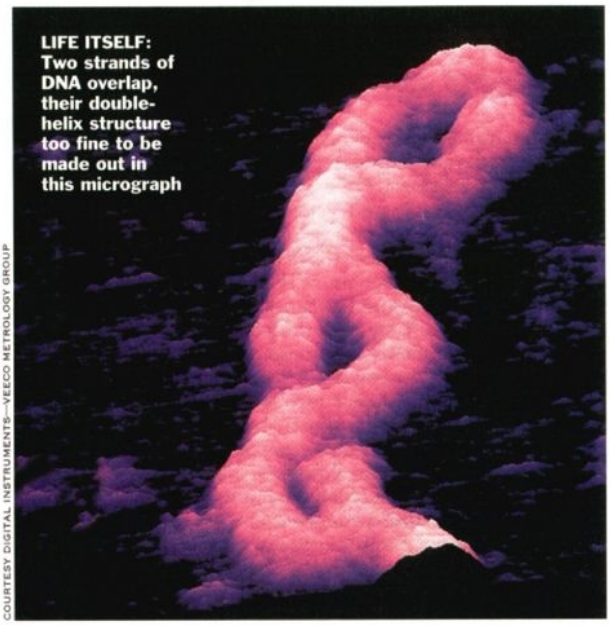
big advances. Cohen's discoveries of prostate-cancer genes are one example. Similarly, the National Center for Biotechnology Information, part of NIH's National Library of Medicine, is using databases of partial gene sequences to zero in on genes that make aberrant proteins in ailments like Parkinson's disease.

Meanwhile, the threat of being upstaged by Venter has put enormous pressure on the Human Genome Project. During a previously scheduled project review last summer, the directors did a thorough re-evaluation of their procedures, soliciting advice from the scientists doing the actual mapping. In the end, the message was clear. Says Collins: "We heard from the users that our current degree of accuracy wasn't needed for many of their strategies."

So the Human Genome Project was recast. Completion was pushed up from 2005 to 2003. And while project scientists had previously been unwilling to release data until they were of high quality, the administrators announced that they would offer up a "working draft" of only moderate precision by 2001. Says Mark Guyer, an assistant director with the NIH's National Human Genome Research Institute: "These data are so rich, it's hard not to extract value from them." But, he admits, "it would not have happened had it not been for the Celera announcement."

Venter wasn't finished, though. Last month it was revealed that the U.S. Department of Energy, whose labs are part of the federal project, was negotiating with Venter to let him do part of the job for it. The cost to the government: zero. That proposal was put on ice by project leaders, supposedly because the DOE had contracted with Venter without checking with other project members, and also out of fear that the release of information to the public might be delayed. Unofficially, it's clear that sour grapes over Venter's latest triumph played a role in their decision.

Government scientists call private efforts pirate operations that may lock up critical data



LIFE ITSELF: Two strands of DNA overlap, their double-helix structure too fine to be made out in this micrograph

COURTESY DIGITAL INSTRUMENTS—VEECO METROLOGY GROUP

Whether it's Venter or the government or some sort of public-private partnership that eventually finishes the job, all the genome mappers agree that once the gene sequence is complete, the next step will be to look into how genes vary from one person to the next. In most diseases, it is probably a conspiracy of several genes and environmental factors that result in illness or death. Through its human-variation project, the NIH hopes to identify genes and sets of genes that only nudge people toward a particular disease.

"This will be our most powerful tool," says Collins. "Finding these weak-susceptibility genes will be moderately useful for predicting risk, but they will be far more useful in allowing us to see the real molecular basis of diseases—all diseases—whether it's multiple sclerosis or brain tumors or diabetes." The truth is that no one can predict exactly what breakthroughs might result from the deciphering of the human genome. As Venter puts it: "It's like it was before electricity. No one could have envisioned personal computers back then."

And for that reason, it's probably just as well that both efforts, public and private, are proceeding in parallel. "The public sector is learning how to produce very high-quality data," says Maynard Olson, director of the University of Washington Genome Center, which is part of the federal project. "You'll never see private companies doing that." If private companies focus first on the most intriguing genes, while government-sponsored scientists sequence the rest, everybody will profit in the end. *—With reporting by Dan Cray/Los Angeles, Andrea Dorfman/New York and Kate Noble/Cambridge*

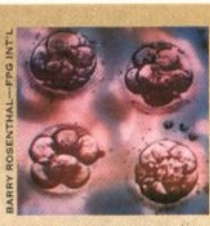
1991 Analyzing chromosomes from women in cancer-prone families, Mary-Claire King, of the University of California, Berkeley, finds evidence that a gene on chromosome 17 causes the inherited form of breast cancer and also increases the risk of ovarian cancer.

JANE SCHERR—UC BERKELEY

1992 The U.S. Army begins collecting blood and tissue samples from all new recruits as part of a "genetic dog tag" program aimed at better identification of soldiers killed in combat.

1992 American and British scientists unveil a technique for testing embryos in vitro for genetic abnormalities such as cystic fibrosis and hemophilia.

1993 After analyzing the family trees of gay men and the DNA of pairs of homosexual brothers, biochemists at the U.S. National Cancer Institute report that at least one gene related to homosexuality resides on the X chromosome, which is inherited from the mother.



BARRY ROSENTHAL—FPG INT'L

1993 George Washington University researchers clone human embryos and nurture them in a Petri dish for several days. The project provokes protests from ethicists, politicians and critics of genetic engineering.

1993 An international research team, led by Daniel Cohen, of the Center for the Study of Human Polymorphisms in Paris, produces a rough map of all 23 pairs of human chromosomes.

1995 Researchers at Duke University Medical Center report that they have transplanted hearts from genetically altered pigs into baboons. All three transgenic hearts survived at least a few hours, proving that cross-species operations are possible.

Who Owns Our Genes?

IT'S NOT FOR NOTHING THAT SCIENTISTS are in such a footrace to get the human genome mapped. There's more than just knowledge at stake, after all—there's money. Who walks away with most of the booty won't be decided in labs or universities, however, but in courts and patent offices.

Though deciphering the entire human genetic blueprint is still a few years away, scientists have begun laying claim to the stretches of DNA whose codes they have succeeded in cracking. In recent years researchers have flooded the U.S. Patent and Trademark Office with applications for thousands of genes and gene fragments—and they have stirred a lot of controversy in the process.

The biggest problem with patenting genes is that while scientists have at least a general idea of what specific strands of genetic coding do, often it's just that—general. Investigators do sometimes succeed in isolating a single, crisp gene with a single known function. Often, however, researchers trying to map genes get no further than marking off fragmentary stretches of DNA that may be thousands of bases in length. These so-called expressed sequence tags may have real genetic information embedded in them, but determining where those nuggets are and what their structure is takes more digging.

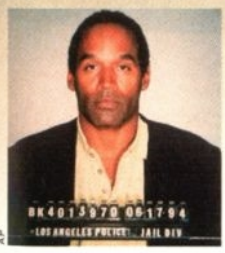
Geneticists have lately been filing patent applications for these ESTs anyway, figuring that it's best to protect their turf now and go spelunking around in it later. In a science that prizes precision above all else, this can be an odd way to do business. "I would guess that in many cases the scientists didn't even examine all the material," says Bruce Lehman, commissioner of the Patent and Trademark Office.

Not only can such filings be sloppy genetics, they can also be bad business. EST applications may lead to so-called submarine patents, claims that are made today and then vanish, only to reappear when some unsuspecting scientist finds something useful to do with genes hidden in the patent. To prevent this, Lehman requires that EST applications include no more than 10 genetic sequences. Each 10 after that requires a separate application—and a separate filing fee. "Companies will now have an incentive to file more selective applications," says Lehman.

More troubling than determining how to patent the genome is the larger question of whether anyone ought to be laying claim to human DNA at all. This is partly an economic issue. If the entire genetic schematic is pre-emptively owned by the research teams studying it now, where is the incentive for independent scientists—often sources of great innovation—to work on it later? Licensing costs, warns Jeffrey Kahn, director of the University of Minnesota's Center for Bioethics, could hold medical progress hostage. Patenting proponents insist that an equally persuasive argument could be made that the large genome-mapping groups need patent protection to make their work worthwhile to them.

Stickier than the economic question is the ethical one. Most of us reflexively shrink from the idea of anyone's owning the rights to any part of the human form. Besides, if the first anatomist to spot, say, the pancreas was not granted title to it, why should modern genome-mapping scientists be able to claim even a single gene? As Kahn points out, "You could patent a system for mining gold from ore. We don't let people patent the gold." That kind of argument is grounded not in law but in the very idea of what it means to be human—an issue that even the highest federal court is not likely to settle. ***—By Jeffrey Kluger***

1995 Former football player O.J. Simpson is found not guilty in a high-profile double-murder trial in which PCR and DNA fingerprinting play a prominent but apparently unpersuasive role.



AP

STEPHEN FERRY—GAMMA LIAISON

1997 Researchers at Scotland's Roslin Institute, led by embryologist Ian Wilmut, report that they have cloned a sheep—named Dolly—from the cell of an adult ewe.

1998 Biologist Craig Venter announces ambitious plans to decode the entire human genome by 2001.

1998 University of Hawaii scientists, using a variation of Wilmut's technique, clone a mouse, creating not only dozens of copies but three generations of cloned clones.

1998 DNA analyses of semen stains on a dress worn by Monica Lewinsky match DNA from a blood sample taken from President Clinton.

REUTERS

1998 DNA testing proves that U.S. President Thomas Jefferson had at least one child with one of his slaves, Sally Hemings.

1998 Two research teams succeed in growing embryonic stem cells.

1998 Scientists at Japan's Kinki University clone eight identical calves using cells taken from a single adult cow.

2003 The Human Genome Project's current target date for sequencing all human DNA.

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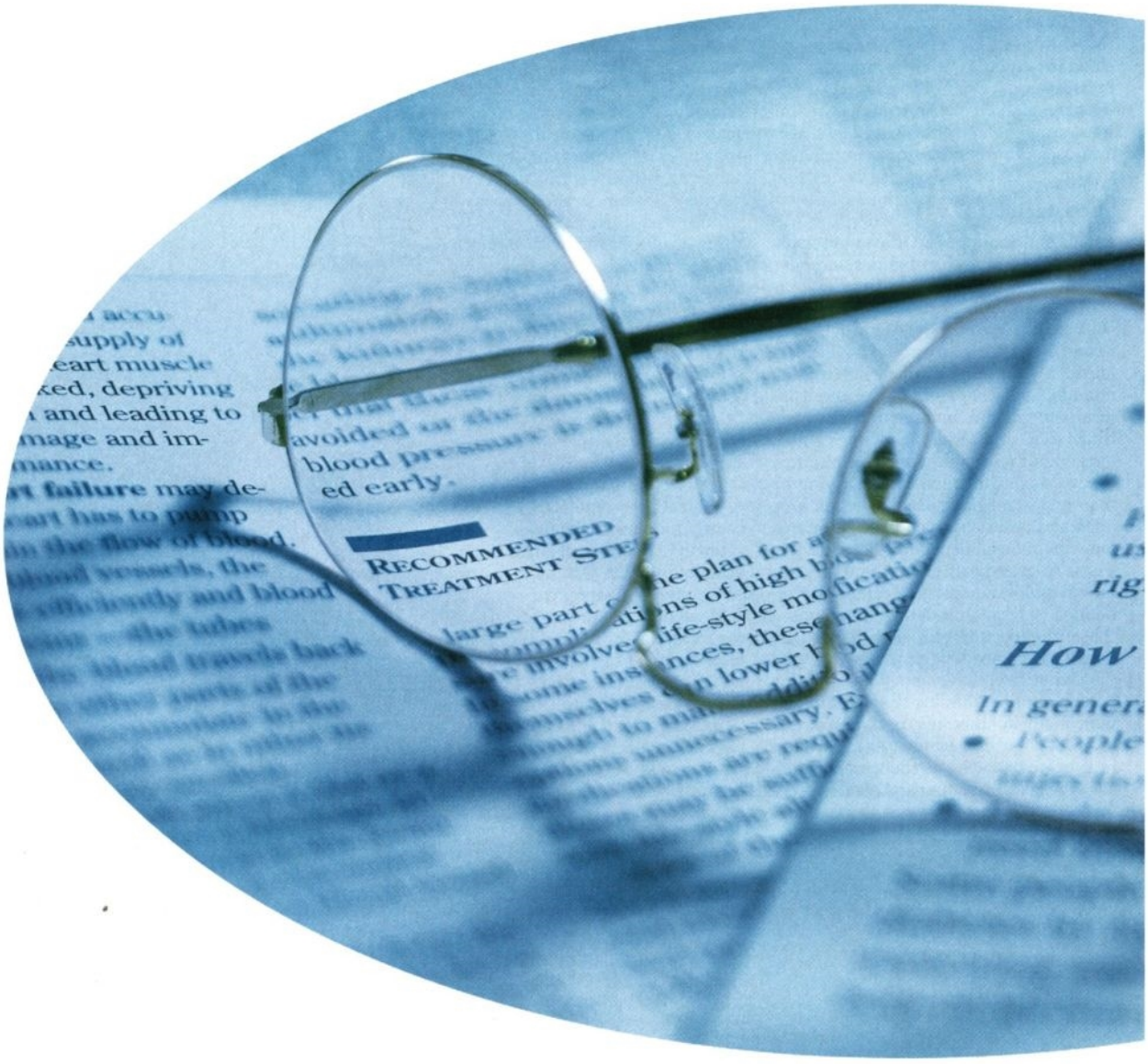

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Craig Venter is a man in a hurry, and now all the genome mappers are operating on Venter time

Gene Maverick

By DICK THOMPSON WASHINGTON

IT WAS YOUR TYPICAL MILLION-DOLLAR SOUTH BEACH BASH: A STAR-STUDDED CROWD GROOVING to the sounds of *Shotgun* rocker Bruce Hornsby at a Gianni Versace mansion. But what was different about this party, thrown last September, was its guest list: 1,800 of the world's leading genomics experts drawn to Miami by a conference sponsored by Craig Venter, the enfant terrible of the gene hunters. Not everyone in the galaxy of genetics stars was there, however. Conspicuously absent was DNA co-discoverer James Watson, a former head of the federal Human Genome Project, who like other scientists in the field has had a long, troubled relationship with the party's host.

Venter's Miami gene festival captured many sides of a complex personality that seems to thrive on rattling the world of molecular biology. In his most recent seismic event, the maverick-millionaire-scientist-cum-rock-fan announced last May that his privately funded lab will decode the entire human genome years faster and for hundreds of million of dollars less than the U.S. government's vaunted Human Genome Project.

It was a brazen challenge to the scientific establishment, but Venter has a genius for making the tools of molecular biology do big things. He has decoded more genes, and faster, than anyone else in the world. He pioneered the use of automated gene sequencers. He developed the most widely used method of tagging bits of genes. And he was first to sequence the genome of an entire living organism. Nearly half the genomes that have been decoded to date were decoded in his lab.

Nonetheless, scientists with the federal project were quick to criticize Venter's new plan. They said that his genome map will be full of holes and that his financial backers will lock it up with patents, blocking the advancement of science.

They may be right. But by throwing the genome program into a competitive race, Venter has forced government-funded gene researchers to rethink their plans. Says Rockefeller University biologist Norton Zinder, who headed the first National Institutes of Health advisory panel on the Human Genome Project and recently signed on to the Venter venture: "Now everybody has awakened."

Driven, impatient, demanding, irritating, Craig Venter has a knack for making the rest of the world run at Venter speed. "I've always felt in a hurry to get things accomplished," he cheerfully confesses. He is in constant motion—lecturing in Europe, raising money on Wall Street, opening satellite centers in California. The closest he comes to relaxing is sailing on his 82-ft. sloop, the *Sorcerer*. Even that's a challenge. "He seldom goes for a day sail," says his wife Claire Fraser, a noted molecular biologist. "When he goes sailing, he's got to cross oceans."

No high-school graduate was ever more unlikely to succeed than Venter. He was a chronic discipline problem—even as a child he refused to take tests—and his parents despaired. In 1964, after being promoted out of high school, Venter moved from his San Francisco home to Southern California, where he dedicated himself to surfing, sailing and the life of a beach bum.

Those carefree days came to an abrupt end when Uncle Sam beckoned and Venter obliged by becoming a Navy hospital corpsman. By 1967, when he was just 21, he was in Vietnam, stationed at the Naval Hospital in Danang. Venter was the senior corpsman in the emergency room during the Tet offensive. For five days he worked around the clock to mend, save or just ease the pain of thousands of young men. Shortly after Tet, when physician Ronald Nadal met him, Venter was in trouble again, following an altercation with a senior officer whom Venter advised to perform, as Nadal tactfully describes it, "a biologically impossible act."

Nadal adopted the ne'er-do-well corpsman, and the two worked closely over the next few months. Impressed by the young man, Nadal urged him to go to college after the war. "You felt this was someone who was not educated but who had a lot of raw intelligence," he says.

"Vietnam changed him," says Fraser. "It impressed on him the idea that time is precious, that you have to make every single minute of every single day count."

Venter decided he would become a doctor and work in the Third World. In a blazing six years, he finished his coursework, published a string of papers, was awarded his Ph.D. and found himself teaching med students. Along the way, he learned that his gifts lay less in medicine than in medical research. In the late '70s he met Fraser. They were married, and except for one brief professional separation have worked side by side ever since.

In the early 1980s, Venter and Fraser were working on cell-surface receptors at the NIH. This was the dawn of the molecular revolution in biology, and the gene was emerging as the key. Finding genes was agonizingly slow work, however; scientists

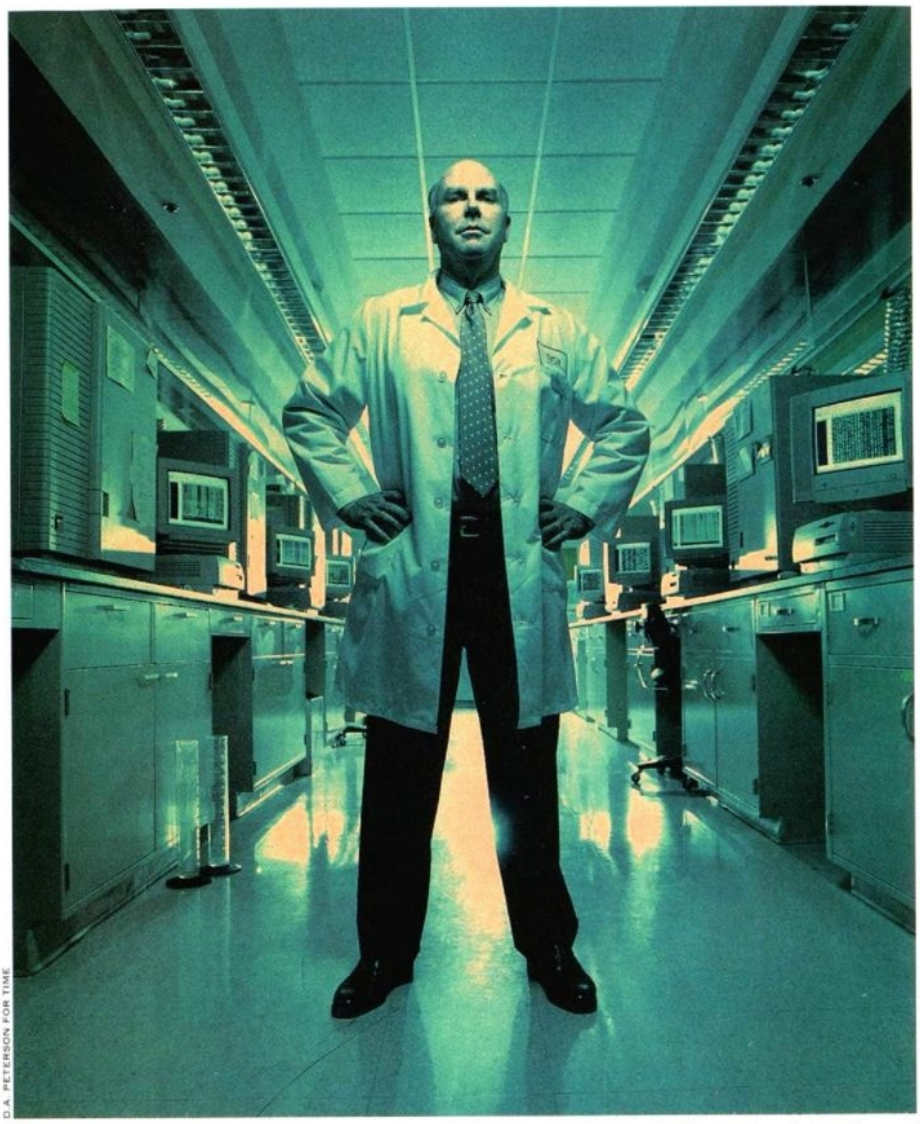
WHAT PEOPLE THINK

The Federal Government is currently spending $3 billion trying to map all human DNA. Do you agree or disagree with this use of taxpayer dollars?

Agree 37% **Disagree** 55%

Some private companies working to discover genes are also trying to get patents on them so they can make money. Do you approve or disapprove of this?

Approve 23% **Disapprove** 71%



D.A. PETERSON FOR TIME

ROBOT ARMY
If Venter wins the genome race, it will be largely thanks to automated sequencers like these

typically spent years locating and decoding a single one.

In 1986 Venter read a paper in the British science journal *Nature* describing a machine that could decode genes automatically. He flew to California and met with one of the machine's designers, Michael Hunkapiller. Within a few months, he had the first automated gene sequencer at the NIH. Within a year, the machine had decoded 100,000 letters in one region of a genome—fast, but not fast enough for Venter.

Then he had an epiphany: he realized that he didn't need to identify those parts of a cell's genome that code for proteins as long as the cell itself can identify them. Venter switched his attention from the DNA blueprint to the RNA templates the cell makes from those blueprints. His task vastly simplified, he began turning out gene sequences at unprecedented rates.

Venter's success shocked and in some cases angered the scientific world. Watson famously dismissed Venter's sequences as work "any monkey" could do, and when their feud over the issue of patents ended, they were both out of the NIH. Watson retreated to Cold Spring Harbor, N.Y., to head the research lab there. Venter started talking to investors.

Venter flourished in the private sector. Backed by venture capitalist Wallace Steinberg, he founded the Institute for Genomic Research (TIGR) and within a year had been transformed from a government scientist with a $2,000 savings account to a millionaire. He gave gifts of stock to his family and Fraser's, and bought the *Sorcerer*. Meanwhile, he continued to pour money into genomics, completing gene maps of the *Haemophilus influenzae* bacterium in 1995, followed by those of *H. pylori*, which causes ulcers, and the syphilis microbe.

Even though TIGR was spewing out gene sequences at unprecedented rates, Venter was still restless. Then Hunkapiller called from his office at Perkin-Elmer to say that he had a new, faster machine he wanted Venter to see. What Venter saw was the future: a gene-mapping computer 50 times as fast as anything running at TIGR. With one of these machines, the 1,000 scientists who had spent 10 years decoding a yeast genome could have completed their work in one day. Emboldened by the new technology, Venter announced his plans to sequence the human genome rapidly. He founded Celera with Perkin-Elmer and promised to publish results freely on a quarterly basis. From now on, Venter said, he was in the information business, selling access to the genomic data he was gathering at breakneck speed.

With prestige and grants on the line, government and academic scientists regrouped and counterattacked. The most important naysayer, as usual, was Watson, but others quickly lined up behind him. Venter's "book of life," said one of the leaders of the federal genome program, would be a *Mad* magazine.

But even his many critics acknowledge that Venter is a scientist with remarkable insight—indeed, a likely Nobel prizewinner. Francis Collins, who took over the Human Genome Project after Watson's departure, concedes that Venter "stirred the pot," while Watson, still Venter's severest critic, is careful to avoid public comment on their feud. But with the race entering its final laps, Venter is prepared to stake everything he has on the outcome. "In three years or so," he promises, "one of us is going to look mighty foolish." ■

The growing power of prenatal genetic tests is raising thorny new questions about ethics, fairness and privacy

Good Eggs, Bad Eggs

By **FREDERIC GOLDEN** LOS ANGELES

THEY WERE HARDLY THE SORT OF COUPLE you would expect to have trouble with prenatal testing. The father, Dallas geneticist Dr. Paul Billings, was the author of pioneering studies about genetic screening and its problems. The mother, Suzi, was also a physician. When she became pregnant at 37, she not only opted for amniocentesis—mainly to check for Down syndrome, an increased risk for children of mothers her age—but also for a newer genetic probe for an inheritable neuromuscular disease. She knew that a member of her family carried the gene for it and realized she might have it too. "It was a straightforward matter and deemed valid by our doctor," says Billings. "But Blue Cross adamantly refused to pay the bill—even though it was only $300."

The Billingses are now the parents of a healthy three-month-old girl. And as well-off professionals, they can afford to brush off the incident as a minor bureaucratic irritation. But for many other would-be parents, the rapidly expanding availability of genetic tests to identify inherited ailments before or after birth often raises issues that are not so easily resolved.

On the contrary, it often opens a Pandora's box of questions that tear not only into pocketbooks but at our psyches: What if the news from a test is bad? Or ambiguous? Should the fetus be aborted? Or should the child be brought into the world in hopes that a cruel disease can be managed or cured? And will insurance coverage be available if the condition was known at birth?

Beyond the poignantly personal dilemmas are broader family and societal issues. If a test is positive, should blood relatives be warned that their genes may contain the same inherited flaw? If so, should such findings become part of a permanent record, like a college transcript or an income tax return? And should doctors alert public health authorities, as they would for contagious conditions such as typhoid, hepatitis and AIDS? More disturbing, isn't there a hint of eugenics in all this picking and choosing, an attempt to shape people to our own genetic prejudices?

Indeed, the almost daily advances in our ability to forecast any of the 4,000 inherited diseases our genes might bequeath us have created such a thorny knot of private, ethical and social issues that the new genetic procedures are the subject of some 20 bills before Congress. In addition, 3% or 4% of the federal investment in the Human Genome Project—about $90 million—is now going to studies seeking to untangle them. One result is the imminent appointment of an 11-member blue-ribbon panel to advise Secretary of Health and Human Services Donna Shalala on how to guide us into this new era of genetic testing.

Testing is, of course, already commonplace. As many as 9 out of 10 pregnant women in the U.S. submit to some prenatal screen-

SILICON GENES Biochips like these from Vysis Inc. may someday be able to analyze your DNA in mere seconds

WILL CROCKETT FOR TIME

ing. Typically, this involves sampling the mother's blood—so-called serum-alpha-fetoprotein testing to seek out telltale proteins that may indicate spina bifida, neural-tube defects or Down syndrome—or looking directly at the fetus with ultrasound scans. For women over 35, doctors usually recommend more invasive procedures in which actual fetal cells are gathered from the womb's amniotic fluid (amniocentesis) or placenta (chorionic villus sampling).

Even so, these tests can spot only visible abnormalities in the 23 pairs of chromosomes we inherit from our parents, such as the extra chromosome associated with Down syndrome, a form of mental retardation, or biochemical errors, such as a reduced level of hex-A enzyme that brings on Tay-Sachs disease, a fatal metabolic disorder. Moreover, the results may be confused by so-called chromosome structural abnormalities—oddball configurations that may or may not have a genetically significant effect, thus exasperating couples who expect clear-cut answers from amniocentesis or CVS.

To look more closely at the baby's genetic prospects, doctors must probe the long stretches of DNA along the chromosomes constituting its genes. Thanks to the spectacular success of molecular biologists in identifying specific disease genes, burgeoning U.S. genetic centers now offer DNA tests for 30 or 40 of the more commonly inherited disorders, including cystic fibrosis, susceptibility to some types of breast cancer, fragile X syndrome (after Down, the most common cause of mental retardation), Huntington's disease, Duchenne muscular dystrophy, and various types of degeneration of the brainstem, spinal cord and peripheral nerves. If you include testable variants of some diseases, such as the many different genetic mutations that can cause cystic fibrosis, the number of available DNA

WHAT PEOPLE THINK

Would you like to know, through genetic profiling, what harmful diseases you might suffer from later in life?

Yes 62% No 34%

Your children might suffer from?

Yes 64% No 33%

probes rises to some 400, with the count growing almost daily. What's more, some tests provide accuracy as high as 99%.

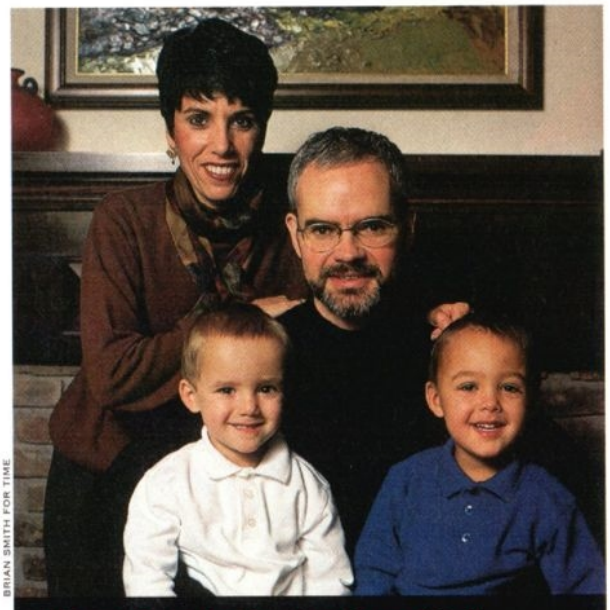
Even more genetic gee-wizardry lies just down the road. Using biochips—thumbnail-size pieces of material imprinted with hundreds of different DNA probes—scientists should be able to identify genetic errors almost as quickly as a supermarket scanner prices a load of groceries. In some systems, the probes use different fluorescent dyes that glow under laser light when they hook up with target genes, allowing sensors to tabulate the results automatically. Genetic researchers are already talking about using "FISH [for fluorescent in-situ hybridization] and chips," as they whimsically call these new tools, to look for any number of genetic characteristics, including the more elusive web of genes that may lurk behind familial patterns of heart disease and stroke, cancer, diabetes, Alzheimer's, various kinds of mental disorders and even gingivitis. Says Dr. Wayne Grody, head of the DNA diagnostic lab at the UCLA Medical Center: "We'll soon be governed by a new paradigm—genomic medicine—with tests and ultimately treatment for every disease linked to the human genome."

WHAT CAN GO WRONG

Some of the genetic disorders that can be detected before birth

DISORDER	INCIDENCE
Cystic fibrosis	1 out of 2,500 white births
Down syndrome	1 out of 800–1,000 births
Duchenne muscular dystrophy	1 out of 3,300 male births
Fragile X syndrome	1 out of 1,500 male births 1 out of 2,500 female births
Hemophilia A	1 out of 8,500 male births
Huntington's disease	4-7 out of 100,000 births
Polycystic kidney disease	1 out of 3,000 births
Sickle-cell anemia	1 out of 400–600 black births
Tay-Sachs disease	1 out of 3,600 Ashkenazi Jewish births

What if the news from a test is bad? Or ambiguous? Should the fetus be aborted?



BRIAN SMITH FOR TIME

When Genetic Testing Says "Go"

Married at 38, Barbara Nastro tried immediately to have children but miscarried again and again. "It was heartbreaking," says the Whitehouse Station, N.J., magazine ad-sales rep. Suspecting that age and the quality of her eggs were the problem, fertility specialists at St. Barnabas Medical Center in Livingston, N.J., recommended a combination of in-vitro fertilization and genetic testing of the fertilized cells called pre-implantation genetic diagnosis (PGD). Nastro hesitated, concerned that the procedure might damage the unborn child. "How perfected was it?" she asked herself. "What would the aftereffect be?" She and her husband spent hours weighing the pros and cons with a genetic counselor, then gave their O.K. Of the 21 eggs harvested from her ovaries, 12 were fertilized with her husband's sperm. Five embryos passed genetic muster and were implanted. In June 1996, Nastro gave birth to healthy fraternal twins, Gabriel and Luke. "We knew PGD was the only answer for us," says the ecstatic mom.

Benefits from this new era are coming fast. Prenatal screening has helped to reduce more than 95% the number of Tay-Sachs births among American Jews of East European descent, a high-risk group. As a result of early identification, a few congenital conditions, such as spina bifida, a disabling hole in the spinal cord, are being treated in the womb by experimental surgery at about seven months. Sex-selection techniques based on in-vitro fertilization can reduce the risk of giving birth to a baby with sex-linked disorders, such as Duchenne muscular dystrophy and hemophilia, which affect only males.

If couples know they carry genes for life-threatening illnesses that they don't want to pass on to the next generation, they can opt for a remarkable procedure called pre-implantation genetic diagnosis (PGD). It starts with standard in-vitro fertilization, in which sperm from the father are mixed with eggs collected from the mother in a Petri dish. Then comes the genetic magic.

The fertilized eggs are subjected to intense DNA analysis. Only those that pass the test are implanted. Says Dr. Jeffrey Botkin, a University of Utah pediatrics professor: "Instead of aborting a fetus, you're flushing down a bunch of 16-cell embryos—which, to a lot of folks [who oppose abortion], is a lot less of a problem."

ONLY A FEW THOUSAND PGDS HAVE BEEN PERFORMED worldwide since Dr. Alan Handyside developed the procedure at London's Hammersmith Hospital in 1989. The majority of candidates for PGD are infertile couples or older women who suffer repeated miscarriages, a condition often due to chromosomal errors easily identified in the embryo stage. But for most couples the cost is prohibitive; a screen for a single disease costs $20,000. Says Santiago Munné of St. Barnabas Medical Center in Livingston, N.J.: "The limit is not that the population doesn't want it; it's that they cannot pay for it. We could do many more diseases if PGD were covered by insurance." In fact, insurance has become a central issue of this brave new world (*see following story*).

Another major concern is privacy. If screening reveals all the faults our flesh may be heir to, can that information be kept secret, so that it won't be used by potential employers or insurers to deny us a job or health coverage? Or, if we let our imaginations fly, by still other types of snoops—for example, an overzealous father eager to check out the genes of a potential son-in-law, just as he once might have checked the suitor's credit rating?

Such scenarios are not science-fiction. With the prestidigitation of gene-amplification, only a single drop of blood or a snippet

of hair or a scraping of skin can reveal the full length of the human genome, including its myriad flaws. And the potential for abusing that information is already here, as a surprised Paul Billings found in surveys of testing abuses that he conducted. "I advertised for people who had had negative experiences with social agencies, insurers or employers after genetic diagnosis, and I was shocked by the response." The most common complaint was against hard-nosed health insurers, but many talked of being denied a job or losing a promotion. Some even reported that they had been prevented from adopting children because of information found in genetic tests. Billings recalls, for example, a couple who had a child with phenylketonuria (PKU), an inherited condition that can lead to retardation but is easily—and inexpensively—treated by diet. "Insurance companies not only refused to write policies for the couple but effectively ostracized the entire family," he says.

Genetic screening is also becoming an issue in the courts, not just as a forensic tool to catch criminals but even to settle private squabbles, says Professor Lori Andrews of Chicago-Kent College of Law. In a custody case in South Carolina, a judge ordered a man's former wife to be tested for Huntington's because it might impair her ability to care for their children. In another case, a manufacturer demanded a genetic test of an ailing boy in order to show that his illness was caused not by the toxicity of substances made by the company but by his genetic predisposition.

Or should the child be brought into the world?

Still more concerns, legal or otherwise, could arise with the increasing availability of tests for so-called low-penetrance genes, such as those associated with breast or colon cancer. These don't necessarily mean that the carrier will be stricken but suggest an increased risk, especially in the presence of certain "co-factors" like poor diet, alcohol or smoking. Such tests are already available for the BRCA1 and BRCA2 breast-cancer genes but at a cost of about $2,700 each, and with their limited predictive abilities, only a few are performed. Still, they raise critical questions for any woman who tests positive. Should she undertake a pre-emptive strike against possible cancer with radical measures like mastectomy and chemotherapy? And if so, will insurers pick up the tab? In the absence of any firm reimbursement policies, says Dr. Ellen Clayton, a pediatrician and lawyer at Vanderbilt University in Nashville, Tenn., "I think you'd have to be nuts to let anybody know [about these genes]."

So far, medicine seems ill equipped to handle the issues spawned by genetic testing. Primary-care physicians, who guard the portals of today's managed-health-care system, rarely have had any training in clinical genetics. "My job is centered almost as much on educating doctors as patients," says genetics counselor Michelle Fox of the UCLA Medical Center. If they uncover a genetic problem in patients, like a family history of muscular dystrophy in a couple who want a child, savvy physicians will enlist a trained specialist like Fox. These specialists can explore with the couple what it means to care for a child with muscular dystrophy (under improved treatment, such children can survive well into middle age).

Unfortunately, there are only about 2,000 counselors nationwide. The only thing most women know about genetic screening is what they learn from pamphlets handed out in the course of routine prenatal care, and too often the message there is sugarcoated. "They talk about 'making your baby better' or 'having a better birth outcome' instead of talking about the fact that this is really a test about selective termination," says medical anthropologist Nancy Press of Oregon Health Sciences University. The failure to make explicit that message—and the decision it forces—says Press, "is simply, clearly, morally wrong."

Sugarcoating the message, however, doesn't change the fact that the message is fundamentally problematic. Genetic testing tells us things about ourselves we may not want to know. Like the twists and turns of the gene-bearing DNA molecule, it brings with it great promise, occasional hidden perils and many, many unresolved questions. *—With reporting by David Bjerklie and Alice Park/New York*

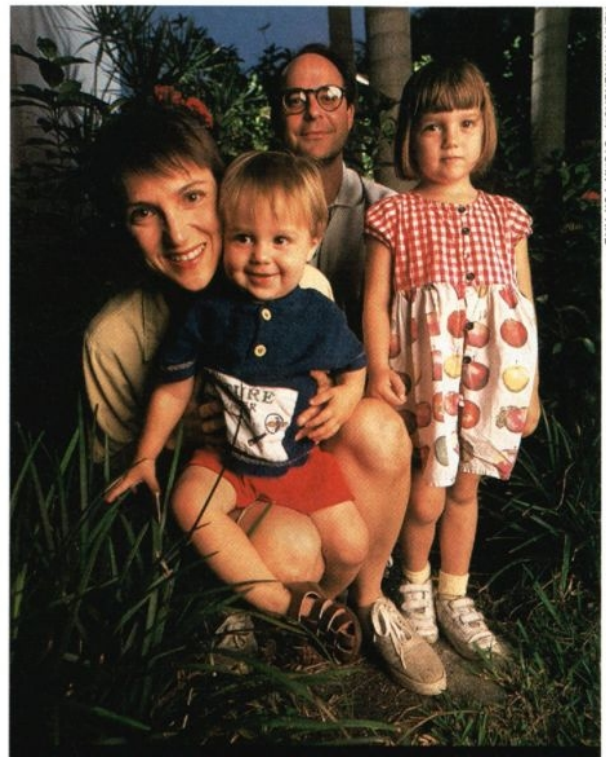
WHAT PEOPLE THINK

Should a person who smokes pay higher insurance rates than a nonsmoker?

Yes 55% No 42%

Should a person whose genetic profile shows potential problems pay higher health-insurance rates than someone whose profile does not?

Yes 8% No 88%



ALAN TANNENBAUM—SYGMA FOR TIME

When Genetic Testing Says "No"

At 37, Kathleen McAuliffe found herself pregnant but in a terrible predicament. An amniocentesis performed at 16 weeks had brought bad news: a large section of chromosome 2 in the fetus' DNA had done a flipflop. The genetic counselor said that if either parent had the same alteration, there was a 10% chance, at most, of a serious birth defect. But chromosome tests on the parents were not reassuring. Neither had the defect.

McAuliffe, a medical writer, knew that even an imperceptible error could signal deformity, if not death. She and her husband debated the risks. He favored continuing the pregnancy, but she had serious doubts and decided to abort. She has since had two healthy babies, a boy and a girl. Though McAuliffe never asked for the results of the autopsy on her aborted fetus, they were sent to her anyway: the baby would have had "crushing" deformities. "If there is a moral to my story," she lamented in the New York *Times*, "it is that there is no moral."

Playing the Odds

Health insurers want to know what's in your DNA

By CHRISTOPHER HALLOWELL

THE DARK SIDE OF GENETIC testing is that information affecting your future health is as valuable to insurers as it is to doctors, but for very different—and disturbing—reasons. Knowing that you are susceptible to breast cancer or diabetes would be invaluable to an HMO looking for ways to screen out riskier candidates and thus keep costs down—and profits up.

PHOTO-ILLUSTRATION FOR TIME BY JOHN BLACKFORD

Insurers say it won't happen. More than 30 states have passed laws prohibiting genetic tests of applicants for jobs or insurance, according to the Council for Responsible Genetics. At least 70 more genetic-discrimination bills are pending in 24 states. Twelve are before the U.S. Congress, and the Health Insurance Portability and Accountability Act of 1996 forbids health insurers to deny insurance based on pre-existing genetic conditions (although raising premiums when renewing insurance is O.K. in some states). "The fears out there are just not reality," says Dean Rosen, senior vice president of policy for the Health Insurance Association of America in Washington, which represents more than 250 health-insurance companies.

The fears, however, persist. Genetic testing is moving inexorably toward becoming standard practice, and it's doubtful that legislation alone can protect against its misuse. The law may prohibit insurers from ordering genetic tests, for example, but in some states nothing prevents them from using tests that are already part of your medical record. "Apply for insurance today, get tested tomorrow," advises a health-insurance executive, only half in jest.

Insurers make their money by spreading risk over as large a population as they can, calculating that the healthy will pay for the sick—and then some. Unless state law prohibits, they can discriminate—legally—by raising premiums for someone who, for example, has suffered a heart attack and is renewing an individual or small-group policy. Access to a growing body of predictive genetic information would permit insurers to weed out further the riskiest, hence costliest clients or at least make them pay more for their coverage even before illness strikes. Little wonder that insurers would like to know, as Rosen puts it, "as much about your medical history as you know."

As testing becomes more sophisticated, coverage based on genetic risks may become untenable, since everyone is likely to be at risk for one disease or another. Until then, says Dr. Paul Billings, a geneticist and medical officer with the Veterans Health Administration, medical insurance must be readily available to all. "I would hope," he says, "that by the end of the century, parceling out a social benefit like insurance based on genetics will be seen as just not appropriate."

Five years ago, most Americans rejected the Clinton Administration's proposals for a larger government role in managing health insurance. But if genetic testing starts to have real impact on their health-care coverage, they could have second thoughts, and may seek refuge in some form of nationalized health insurance. In that case, it will be up to the insurance industry to offer a free-market alternative that Americans find palatable. ■

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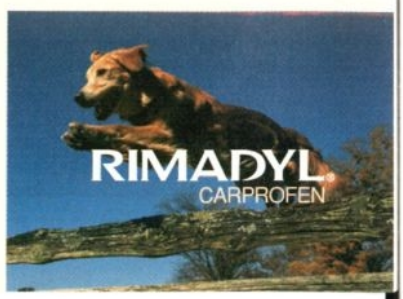
- ☐ Yes ☐ No Is your dog slow to rise from a resting position?

If you answered yes to any of these questions, ask your veterinarian to examine your dog for arthritis.
See brief summary on adjacent page for important information.
1. Data on file, Pfizer Animal Health.



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Genetic fingerprinting is already being used to identify criminals. Can the rest of us be far behind?

DNA Detectives

By JEFFREY KLUGER

IN OCTOBER A 24-YEAR-OLD WOMAN WHO HAD BEEN COMATOSE FOR MORE THAN THREE YEARS gave birth to a baby girl. It was only a few days before the delivery that the staff at the woman's nursing home in Lawrence, Mass., even discovered that she was pregnant. Under the circumstances, the pregnancy had to have been the result of rape; yet the woman was uniquely unable to name her assailant. If she couldn't speak, however, the blood of her daughter could. Shortly after the baby's birth, the police drew a sample of the infant's blood, then took voluntary samples from male relatives of the woman as well as from nursing-home personnel and others who might have had access to her. Comparing the men's DNA with the baby's, they figured, could lead them to the rapist.

While the genetic dragnet cast over Lawrence has not yet yielded any arrests, it has led to controversy. Over the past decade, as anybody who followed the O.J. Simpson trial can attest, DNA profiling has become almost as important a part of crime fighting as fingerprinting. But even as technology pushes forensic science forward, the Constitution has worried it back. The Fourth Amendment guarantees citizens protection from unreasonable searches and seizures, and although the Founding Fathers didn't contemplate strands of DNA when drafting the Bill of Rights, what search could be more invasive than an assay of our very genes?

In Lawrence the question is being raised anew, as men—all but one of them presumably innocent—weigh the ease of submitting to a DNA test against their right to refuse and the suspicion that would be raised if they did. It's a problem that is becoming more and more familiar—and, for civil libertarians, cause for more and more alarm. "These are technologies in which powerful organs in society control members with less power," frets Philip Bereano, a member of the American Civil Liberties Union's board of directors. "They are inherently violative of civil rights."

The power of DNA technology expanded exponentially last fall when the FBI activated its new Combined DNA Index System. A database containing the gene prints of 250,000 convicted felons—as well as 4,600 DNA samples left behind at the scene of unsolved crimes—the system acts as a sort of investigatory intranet through which law-enforcement officials can surf when trying to match a known criminal to a crime.

To streamline sampling, the system identifies subjects not by their entire genetic blueprint but by tiny stretches of DNA coding, known as short tandem repeats that are just two to seven base-pairs long. Though little more than genetic gibberish, STRs yield remarkably accurate results. If three of the ministrands match a suspect's, the likelihood is 2,000 to 1 that police have the right person. Nine matches boost the odds to 1 billion to 1. FBI sampling rules require no fewer than 13 matches. "Its success as a crime-fighting tool is incredible," says Christopher Asplen, director of a national DNA-study commission.

Too incredible for some people's taste, however. Once a database like this is assembled, civil rights advocates argue, it is unlikely to be disassembled, and it is only a matter of time before data grow to include not just wrongdoers but also law-abiding citizens. Proponents of DNA testing dismiss this as libertarian alarmism, but experience suggests otherwise.

In December the police commissioner of New York City recommended that anyone even arrested for a crime—never mind convicted of one—be required to submit a routine DNA sample. In England, where a genetic database has operated since 1995, suspects are routinely screened this way—more than 360,000 gene prints are online—though police do promise that such profiles will be scrubbed from the record if the person is cleared. English officials investigating a crime in a small town sometimes perform mass screenings in which thousands of people are asked to surrender a mouth swab full of DNA. The law gives anyone the right to decline, but as residents of Lawrence, Mass., are learning, no law can prevent the slit-eyed look police give a person who actually chooses to exercise that right. "There is no such thing as a technology like this without an ideology of surveillance and control behind it," says Bereano.

The problem for Bereano and other detractors is that DNA technology works. In England as many as 500 matches are made a week between database entries and samples taken from crime scenes. When mass sweeps are conducted, the police claim a 70% success rate in cracking the crime they're investigating. In the U.S., where the months-old national database has barely got on its feet, the FBI claims that 200 outstanding cases have already been solved. What's more, on occasion, DNA sampling benefits not only the people investigating crimes but also the people convicted of them. Since 1976, 75 death-row inmates have been spared execution in the U.S. when their convictions were overturned. At least 10 of the reversals came on the strength of new DNA evidence.

WHAT PEOPLE THINK

Should the police be allowed to collect DNA information from suspected criminals, as they currently do with fingerprints?

Yes 66% **No 29%**

Is it a good or a bad idea for the FBI to create a DNA database with information gathered from suspected criminals and crime scenes throughout the country?

Good Idea 71% **Bad Idea 24%**

PHOTO-ILLUSTRATION FOR TIME BY AMY GUIP

This kind of investigatory yin and yang is keeping opponents of DNA fingerprinting mollified—but for how long? Now that the gene genie is out of the bottle, there may be little that can be done to stuff it back in. Scientists in the U.S. and England already speak dreamily of moving beyond testing STRs alone, expanding their work to sample other—more richly encoded—areas of the genome. Kevin Sullivan of England's Forensic Science Service predicts that within a decade researchers may be able to use DNA analysis to draw a sort of genetic police sketch of a suspect's appearance, including build, race, facial shape and even inherited physical defects.

The most complex traits, of course, would be the ones even the best detectives would have a hard time seeing: personality traits. If temperament is at least partly determined by genetic hardwiring, somewhere in the vast tangle of human DNA there must be strands that influence behavior—including criminal behavior.

The problem is, If you could locate such genes, what would you do with that knowledge? Should you incarcerate people for crimes they haven't yet committed but are genetically predisposed to commit? Is it possible to fix such miswired genes, and if so, should you try? The possibility of mucking about with such fundamental genetic coding gives a lot of people existential shivers—and it should. "This is the kind of technology that would flourish in an Orwellian society," says Bereano.

For now there's nothing to suggest that things are nearly so dire: DNA fingerprinting has been used for years, and so far it is only wrongdoers who have real cause to wish it hadn't. But when it comes to scientific advances, human beings have often been a slapdash species—racing out ahead with a new technology before fully appreciating its power. If DNA fingerprinting should get into the wrong hands, society's law-abiding members may find they have more in common with its lawbreakers than they ever dreamed possible. —***Reported by Melissa August/Washington and Helen Gibson/London***

Parents can now pick a kid's sex and screen for genetic illness. Will they someday select for brains and beauty too?

Designer Babies

By MICHAEL D. LEMONICK

UNTIL JUST A FEW YEARS AGO, MAKING A BABY BOY OR A BABY GIRL WAS PRETTY MUCH A HIT-OR-miss affair. Not anymore. Parents who have access to the latest genetic testing techniques can now predetermine their baby's sex with great accuracy—as Monique and Scott Collins learned to their delight two years ago, when their long-wished-for daughter Jessica was born after genetic prescreening at a fertility clinic in Fairfax, Va.

And baby Jessica is just the beginning. Within a decade or two, it may be possible to screen kids almost before conception for an enormous range of attributes, such as how tall they're likely to be, what body type they will have, their hair and eye color, what sorts of illnesses they will be naturally resistant to, and even, conceivably, their IQ and personality type.

In fact, if gene therapy lives up to its promise, parents may someday be able to go beyond weeding out undesirable traits and start actually inserting the genes they want—perhaps even genes that have been crafted in a lab. Before the new millennium is many years old, parents may be going to fertility clinics and picking from a list of options the way car buyers order air conditioning and chrome-alloy wheels. "It's the ultimate shopping experience: designing your baby," says biotechnology critic Jeremy Rifkin, who is appalled by the prospect. "In a society used to cosmetic surgery and psychopharmacology, this is not a big step."

The prospect of designer babies, like many of the ethical conundrums posed by the genetic revolution, is confronting the world so rapidly that doctors, ethicists, religious leaders and politicians are just starting to grapple with the implications—and trying to decide how they feel about it all.

They still have a bit of time. Aside from gender, the only traits that can now be identified at the earliest stages of development are about a dozen of the most serious genetic diseases. Gene therapy in embryos is at least a few years away. And the gene or combination of genes responsible for most of our physical and mental attributes hasn't even been identified yet, making moot the idea of engineering genes in or out of a fetus. Besides, say clinicians, even if the techniques for making designer babies are perfected within the next decade, they should be applied in the service of disease prevention, not improving on nature.

But what doctors intend is not necessarily what's going to happen. Indeed, the technology that permitted the Collinses family to pick the sex of their child was first used to select for health, not gender per se. Adapting a technique used on livestock, researchers at the Genetics & IVF Institute in Fairfax took advantage of a simple rule of biology: girls have two X chromosomes, while boys have one X and one Y. The mother has only Xs to offer, so the balance of power lies with the father—specifically with his sperm, which brings either an X or a Y to the fertilization party.

As it happens, Y chromosomes have slightly less DNA than Xs. So by staining the sperm's DNA with a nontoxic light-sensitive dye, the Virginia scientists were able to sort sperm by gender—with a high rate of success—before using them in artificial insemination. The first couple to use the technique was looking to escape a deadly disease known as X-linked hydrocephalus, or water on the brain, which almost always affects boys.

But while the technique is ideal for weeding out this and other X-linked disorders, including hemophilia, Duchenne muscular dystrophy and Fragile X syndrome, most patients treated at Genetics & IVF want to even out their families—a life-style rather than a medical decision. The Fairfax clinic has been willing to help, but such a trend doesn't sit well with some other practitioners. "Our view at the moment," says Dr. Zev Rosenwaks, director of the Center for Reproductive Medicine and Infertility at Cornell Medical Center in New York City, "is that these techniques should be used for medical indications, not family balancing."

But now that parents know that the technology is available, and that at least some clinics will let them choose a child's gender for nonmedical reasons, it may be too late to go back. In a relatively short time, suggests Princeton University biologist Lee Silver, whose book *Remaking Eden* addresses precisely these sorts of issues, sex selection may cease to be much of an issue. His model is in vitro fertilization, the technique used to make "test-tube" babies. "When the world first learned about IVF two decades ago," he says, "it was horrifying to most people, and most said that they

WHAT PEOPLE THINK

If you could choose traits for your baby, would you choose to:

	Yes
Rule out a fatal disease	60%
Ensure greater intelligence	33%
Influence height or weight	12%
Determine sex	11%

Should parents with genetically linked diseases be required to test their children for them?

Yes 39% No 55%

Illustrations for TIME by John Craig

wouldn't use it even if they were infertile. But growing demand makes it socially acceptable, and now anybody who's infertile demands IVF."

That's not to say in vitro fertilization hasn't created its own set of ethical problems, including custody battles over fertilized embryos that were frozen but never used, questions about what to do with the embryos left over after a successful pregnancy, and the increased health risks posed by multiple births. Yet no one is suggesting the practice be stopped. Infertile couples would never stand for it.

Sex selection will undoubtedly raise knotty issues as well. Societies that value boys more highly than girls, including China and India, are already out of balance; this could tip the scales even further. Such an outcome is unlikely in the U.S., where surveys show that equal numbers of parents want girls as boys. But the same polls report that Americans believe an ideal family has a boy as the oldest child. Boys often end up being more assertive and more dominant than girls, as do firstborn children; skewing the population toward doubly dominant firstborns could make it even harder to rid society of gender-role stereotypes.

WHAT PEOPLE THINK

If you had the gene for an incurable life-threatening disease, would you have your unborn child tested for the disease?

Yes 70% No 26%

If the test showed that the baby would have the disease, would you consider ending the pregnancy through abortion?*

Yes 39% No 48%

*Asked of those who would have the child tested

THE ETHICAL ISSUES RAISED BY TECHNIQUES EMERGING from the genetics labs are likely to be even more complex. What if parents can use preimplantation genetic diagnosis to avoid having kids with attention-deficit disorder, say, or those predestined to be short or dullwitted or predisposed to homosexuality? Will they feel pressure from friends and relations to do so? And will kids who are allowed to be born with these characteristics be made to feel even more like second-class citizens than they do now?

Even thornier is the question of what kinds of genetic tinkering parents might be willing to elect to enhance already healthy children. What about using gene therapy to add genes for HIV resistance or longevity or a high IQ? What about enhancements that simply stave off psychological pain—giving a child an attractive face or a pleasing personality? No one is certain when these techniques will be available—and many professionals protest that they're not interested in perfecting them. "Yes, theoretically you could do such things," says Baylor University human-reproduction specialist Larry Lipshultz. "It's doable, but I don't know of anyone doing it."

Sooner or later, however, someone will do it. In countries with national health services, such as Canada and Britain, it tends to be easier to dictate what sorts of genetic enhancement will be permitted and what will be forbidden. But in the U.S., despite the growth of managed care, there will always be people with enough money—or a high enough limit on their credit cards—to pay for what they want. "Typically," says Princeton's Silver, "medical researchers are moved by a desire to cure disease more effectively. Reprogenetics [a term Silver coined] is going to be driven by parents, or prospective parents, who want something for their children. It's the sort of demand that could explode."

Silver even contemplates a scenario in which society splits into two camps, the "gen-rich" and the "gen-poor," those with and those without a designer genome. The prospect is disturbing, but trying to stop it might entail even more disturbing choices. "There may be problems," admits James Watson, whose co-discovery of the structure of DNA in 1953 made all this possible. "But I don't believe we can let the government start dictating the decisions people make about what sorts of families they'll have." —***Reported by David Bjerklie and Alice Park/New York and Dick Thompson/Washington***

Parents may go to fertility clinics and pick from a list of options the way car buyers orde

Who Gets the Good Genes?

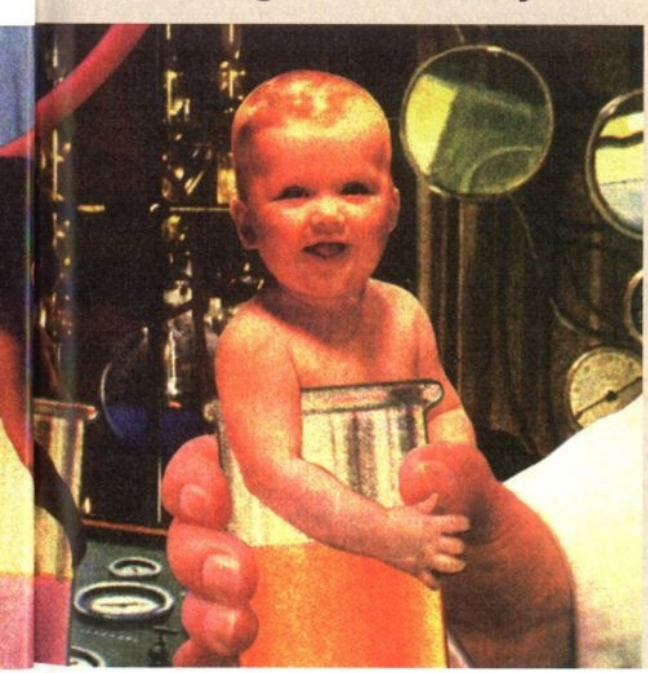
By ROBERT WRIGHT

IN THE 1932 NOVEL *BRAVE New World,* Aldous Huxley envisioned future childbirth as a very orderly affair. At the Central London Hatchery and Conditioning Center, in accordance with orders from the Social Predestination Room, eggs were fertilized, bottled and put on a conveyor belt. Nine months later, the embryos—after "decanting"—were babies. Thanks to state-sponsored brainwashing, they would grow up delighted with their genetically assigned social roles—from clever, ambitious alphas to dim-witted epsilons.

Ever since publication of Huxley's dystopian novel, this has been the standard eugenics nightmare: government social engineers subverting individual reproductive choice for the sake of an eerie social efficiency. But as the age of genetic engineering dawns, the more plausible nightmare is roughly the opposite: that a laissez-faire eugenics will emerge from the free choices of millions of parents. Indeed, the only way to avoid Huxleyesque social stratification may be for the government to get into the eugenics business.

Huxley's scenario made sense back in 1932. Some American states were forcibly sterilizing the "feebleminded," and Hitler had praised these policies in *Mein Kampf.* But the biotech revolution that Huxley dimly foresaw has turned the logic of eugenics inside out. It lets parents choose genetic traits, whether by selective abortion, selective reimplanting of eggs fertilized in vitro or—in perhaps just a few years—injecting genes into fertilized eggs. In Huxley's day eugenics happened only by government mandate; now it will take government mandate—a ban on genetic tinkering—to prevent it.

er air conditioning and chrome-alloy wheels



An out-and-out ban isn't in the cards, though. Who would try to stop parents from ensuring that their child doesn't have hemophilia? And once some treatments are allowed, deciding where to draw the line becomes difficult.

The Bishop of Edinburgh tried. After overseeing a British Medical Association study on bioethics, he embraced genetic tinkering for "medical reasons," while denouncing the "Frankenstein idea" of making "designer babies" with good looks and a high IQ. But what is the difference? Therapists consider learning disabilities to be medical problems, and if we find a way to diagnose and remedy them before birth, we'll be raising scores on IQ tests. Should we tell parents they can't do that, that the state has decided they must have a child with dyslexia? Minor memory flaws? Below-average verbal skills? At some point you cross the line between handicap and inconvenience, but people will disagree about where.

If the government does try to ban certain eugenic maneuvers, some rich parents will visit clinics in more permissive nations, then come home to bear their tip-top children. (Already, British parents have traveled to Saudi Arabia to choose their baby's sex in vitro, a procedure that is illegal at home.) Even without a ban, it will be upper-class parents who can afford pricey genetic technologies. Children who would in any event go to the finest doctors and schools will get an even bigger head start on health and achievement.

This unequal access won't bring a rigid caste system à la *Brave New World.* The interplay between genes and environment is too complex to permit the easy fine-tuning of mind and spirit. Besides, in vitro fertilization is nobody's idea of a good time; even many affluent parents will forgo painful invasive procedures unless horrible hereditary defects are at stake. But the technology will become more powerful and user friendly. Sooner or later, as the most glaring genetic liabilities drift toward the bottom of the socioeconomic scale, we will see a biological stratification vivid enough to mock American values.

Enter the government. The one realistic way to avoid this nightmare is to ensure that poor people will be able to afford the same technologies that the rich are using. Put that way, it sounds innocent, but critics will rightly say it amounts to subsidizing eugenics.

State involvement will create a vast bioethical quagmire. Even if everyone magically agrees that improving a child's memory is as valid as avoiding dyslexia, there will still be things taxpayers aren't ready to pay for—genes of unproven benefit, say, or alterations whose downsides may exceed the upside. (The tendency of genes to have more than one effect—pleiotropy—seems to be the rule, not the exception.) The question will be which techniques are beyond the pale. The answers will change as knowledge advances, but the arguments will never end.

In *Brave New World,* state-sponsored eugenics was part of a larger totalitarianism, a cultural war against family bonds and enduring romance and other quaint vestiges of free reproductive choice. The novel worked; it left readers thinking that nothing could be more ghastly than having government get into the designer-baby business. But if this business is left to the marketplace, we may see that government involvement, however messy, however creepy, is not the creepiest alternative. ■

Gene therapy, heralded in the early 1990s, then stalled by one setback after another, is finally starting to live up to its promise

Fixing the Genes

By LEON JAROFF

EIGHT YEARS AFTER THE HEART-BYPASS OPERATION THAT SAVED HIS LIFE, FLOYD STOKES WAS in deep trouble again. His angina had returned with a vengeance. He was gulping nitroglycerine tablets and was virtually incapacitated, unable to do simple chores on his Seminole, Texas, ranch. Too far gone for another bypass, he had a choice, as he puts it, of "just waiting for death or trying to do something about it."

Stokes chose to survive. He volunteered to take part in a novel clinical trial about to be conducted on heart patients by Dr. Jeffrey Isner at the St. Elizabeth Medical Center in Boston. To his surprise, he was accepted. Last May he flew to Boston, where a solution containing billions of copies of a gene that triggers blood-vessel growth was injected directly into his heart.

Within three weeks, Stokes was feeling better and now, at 58, he is back at work on a normal, nitroglycerine-free routine. "I ride horses and I run tractors," he says. "You have to be in pretty good shape to do what I do." As it turned out, all 16 heart patients in Isner's trial showed improvement, and six are entirely free of pain.

The St. Elizabeth clinical trial is one of some 300 similar types of procedures being performed today on more than 3,000 patients around the world. These numbers reflect a growing optimism that gene therapy, a medical discipline that emerged with great fanfare in the early 1990s but fell out of favor during its adolescence, is finally coming of age. "Twenty years from now gene therapy will have revolutionized the practice of medicine," predicts Dr. W. French Anderson, director of gene therapy at the University of Southern California medical school, who is perhaps the most outspoken champion of this slowly maturing medical art. "Virtually every disease will have gene therapy as one of its treatments."

Gene therapy, simply defined, is the placement of beneficial genes into the cells of patients. By introducing the gene and consequently the protein it produces, says Inder Verma, a professor at the Salk Institute in La Jolla, Calif., "you either eliminate the defect, ameliorate the defect, slow down the progression of the disease or in some way interfere with the disease."

The initial goals of gene therapists were to cure relatively straightforward genetic disorders, such as Huntington's disease and sickle-cell anemia, that are caused by a single defective gene. The strategy was simple: substitute a normal gene for a faulty one. But scientists quickly realized that adding genes to cells could also impart new functions to those cells. That may lead to the genetic treatment of a host of other disorders, including heart disease and many forms of cancer.

But how do you get a new gene into the nucleus of a cell? The trick, researchers discovered early on, is to take advantage of the infectious power of viruses; burrowing into cells is second nature to them. A virus is nothing more than a tiny strip of DNA or RNA crammed into a protein envelope. Using the tools of molecular biology, scientists render the virus harmless by deleting some or all of its genes, splicing the therapeutic gene into the remaining genetic material and, in a laboratory Petri dish, mixing it with human cells. The altered virus, now called a carrier or vector, can deliver the therapeutic gene into the nucleus with great dispatch.

"You can do spectacular things with cells in a laboratory dish," explains Anderson. "You can easily get the genes in, change the cell's properties and do other things that ought to enable you to treat disease successfully." That is precisely what Anderson and his colleagues did eight years ago in the first approved use of gene therapy, when they removed blood cells from a young patient, genetically altered them with a viral vector and infused them back into her bloodstream. (*See box.*)

But could the same be done directly to cells within the human body? "That's where we hit the wall in the early 1990s," recalls Dr. James Wilson, director of the Institute for Human Gene Therapy at the University of Pennsylvania. One problem was that the body's immune system regarded the viral carriers as foreign invaders, and its response caused inflammation and swelling at the injection site. The antibodies that developed in response to the virus caused further difficulties. "In a very unfortunate turn of events," Wilson explains, "the patients would become immune against the therapy."

In an early gene-therapy trial for cystic fibrosis, inflammation caused by the viral carrier, an altered adenovirus, was so severe that the FDA ordered a halt to the effort, casting a pall over all the other trials—and the field in general. More problems plagued the researchers. In many cases the implanted genes failed to "turn on," or express

WHAT PEOPLE THINK

Should the government regulate:

Using gene therapy—that is, altering genes to cure or prevent diseases?

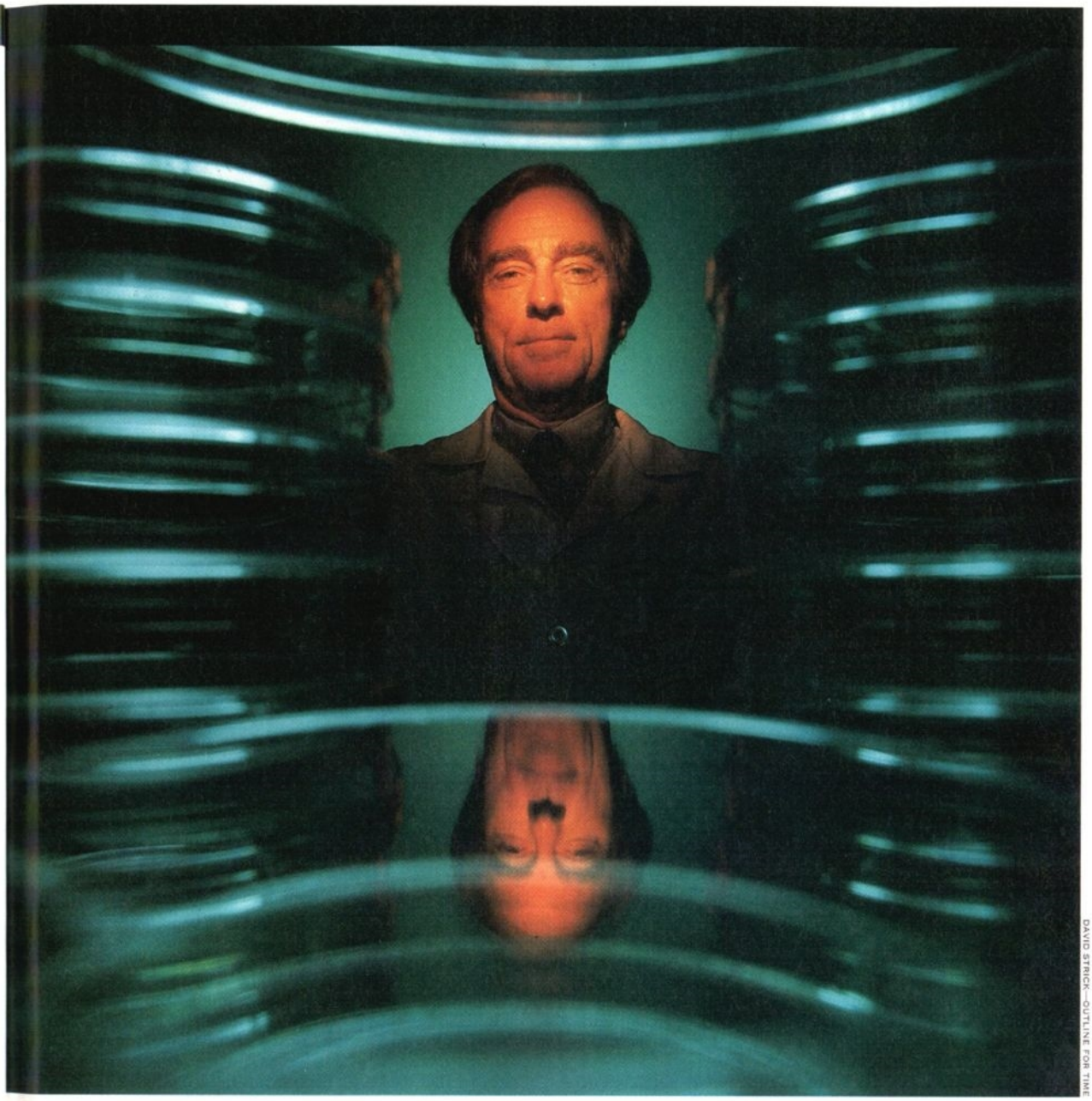
Yes 62% No 30%

Cloning of whole animals?

Yes 47% No 47%

Using genetic testing to pick the traits in unborn children?

Yes 46% No 49%



DAVID STRICK—OUTLINE FOR TIME

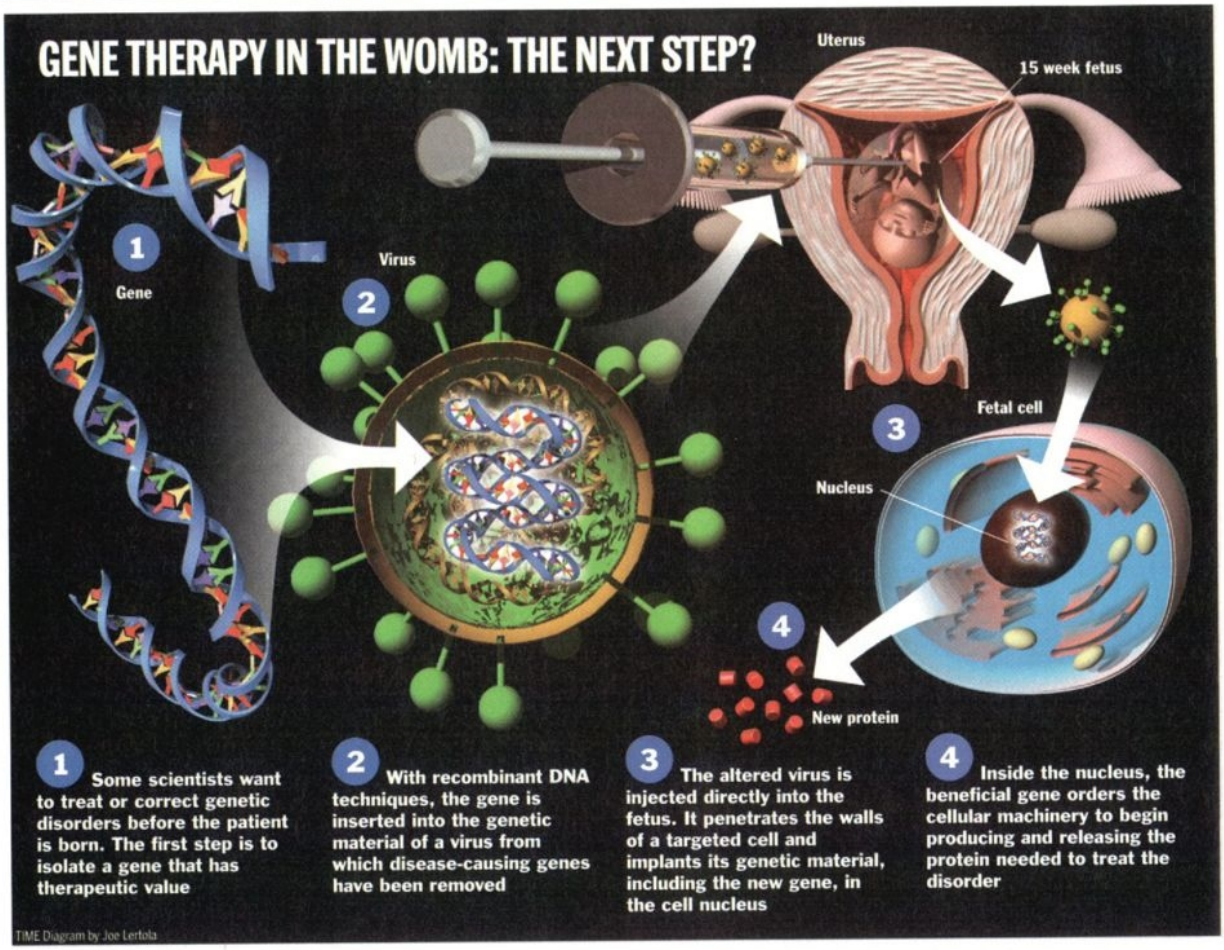
GENE PIONEER
Tall stacks of Petri dishes hold genetically altered cells in Dr. Anderson's U.S.C. medical school lab

themselves, and were unable to command the cells to produce the protein they were supposed to provide. Some operated for a while and then inexplicably shut down.

As a result, many gene-therapy trials failed during what the FDA calls Phase I, in which the safety of the procedure is evaluated on a handful of patients. Others proved ineffective and faltered during Phase II trials, which test a larger group to determine the efficacy of the therapy. And apparently only one trial has so far weathered Phase III, which calls for a larger number of patients and a statistical analysis of the results before the FDA gives its approval for general use.

That trial, being conducted by GTI-Novartis in Gaithersburg, Md., uses an ingenious technique to attack brain tumors. After re-engineering a retrovirus—an RNA virus that invades only cells that are in the process of dividing—the doctors outfitted it with a gene from the herpes virus and injected it into the brain. Because virtually the only cells that divide in the brain are tumor cells, the retroviruses infected them alone, inserting the herpes gene into their nuclei. As this gene expressed itself, it made the tumor cells sensitive to the herpes drug ganciclovir. When the drug was then administered to the patient, says Anderson, it "made the tumor cells commit suicide." But here there were troublesome side effects.

Clearly, gene therapy is not yet a panacea. Anderson concedes that except for reports of individual patients being helped, "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease."



Most researchers in the field agree that the adenovirus and retrovirus vectors are imperfect, to say the least. In addition to having immunological side effects, both lack the carrying capacity to accommodate the larger, more complex genes that would be useful in therapy. "There are only three problems in gene therapy," says Salk's Verma, "delivery, delivery and delivery. It isn't going to be a problem to make gene therapy work—if we have an appropriate set of tools to deliver the genes."

FOR HIS HEART-PATIENT TRIAL, ST. ELIZABETH'S ISNER FOUND a novel way around the delivery problem. Eschewing virus carriers, he fashioned a construct called "naked DNA." It consists of part of a human gene called VEG-F, which stimulates the growth of blood vessels, and includes its signal segments. These segments, Isner explains, "order the cell, once it has manufactured the gene product, to export it from the cell."

In his Phase I trial, Isner injected a saline solution containing his naked DNA through a small "keyhole" incision in the chest of his heart patients and directly into their heart muscle. A few weeks later, tests on everyone in the trial group showed greatly improved blood flow to the heart muscle though tiny new blood vessels that bypassed clogged arteries.

How does the naked DNA, without viral assistance, penetrate the walls of the heart-muscle cells? "To be perfectly honest," Isner confesses, "no one really understands how it gets there." But unlike most other therapeutic genes, which must find their way into millions of cells to have a therapeutic effect, VEG-F needs to invade only relatively few. Its protein product, issuing from the cell, can act on untold numbers of surrounding, untreated cells. Quips Isner in a parody of the Marine Corps slogan, "All we're looking for are a few good cells."

The fact that the VEG-F gene seems to turn off after three or four weeks makes little difference in this trial because the new blood vessels have already sprouted and remain in place. Still, for this and other reasons, the naked-DNA approach is applicable to only a handful of disorders.

For the vast majority of other trials, scientists are hard at work developing a new generation of viral vectors. One promising candidate, says Pennsylvania's Wilson, is the AAV (adeno-associated virus), a small, benign human virus that does not seem to cause any disease. "It doesn't elicit the same kind of inflammatory response that the other vectors do," Wilson explains. "It's somehow evolved the way to get around that." The AAV also efficiently insinuates itself into nondividing cells and, in tests with monkeys and mice, has

"We're talking about a revolutionary approach to therapy, and we're only eight years into it."

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Success Stories

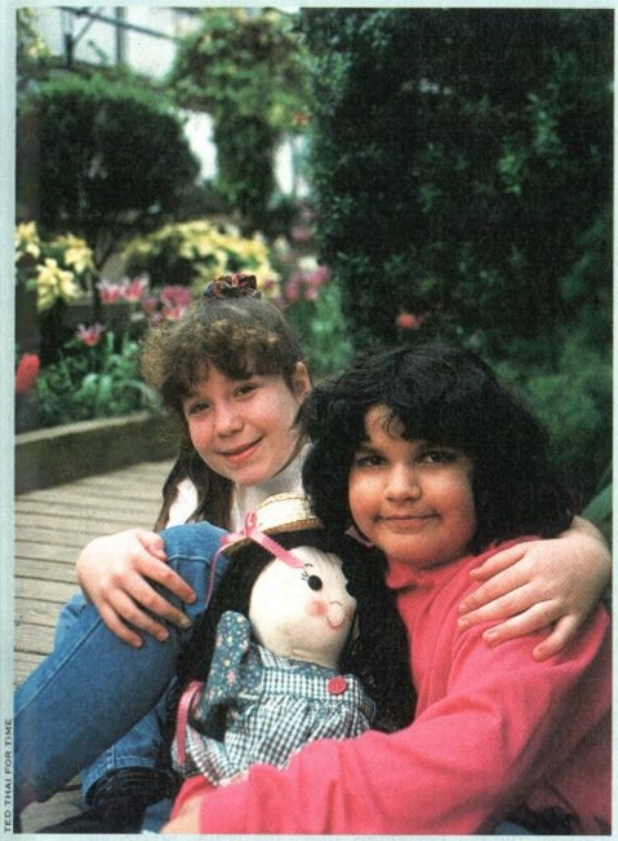
The verdict on the pioneering children of gene therapy: so far, so good

TO ALL OUTWARD APPEARances, Ashanthi ("Ashi") DeSilva is a normal, healthy 12-year-old who loves sports and would rather play basketball than do her seventh-grade homework. But Ashi holds a unique place in medical history: she is the first recipient of successful gene therapy.

Ashi was born with a rare, inherited disorder called ADA deficiency, the disease that claimed the life of the famed "bubble boy" in 1984. Because of a faulty gene, the T cells of her immune system were unable to produce an enzyme, ADA, necessary for their survival. As they died off, Ashi's immune system virtually shut down, leaving her vulnerable to a host of common childhood diseases, some of which could have killed her.

In 1988, when she was two years old, Ashi began taking PEG-ADA, a newly developed drug that consists of the missing enzyme protected by a chemical sheath that enables it to function in the bloodstream for days. While the drug requires weekly injections for life at an annual cost of more than $60,000, it has enabled most of the handful of ADA-deficient children to survive. However, it provided only marginal help for Ashi, and she began to fail.

Ashi's deteriorating condition made her eligible for a landmark experiment proposed by researchers at the National Institutes of Health. In September 1990 a team led by Drs. W. French Anderson and R. Michael Blaese extracted T cells from Ashi and exposed them to mouse



TED THAI FOR TIME

LUCKY KIDS **DeSilva and Cutshall during a 1993 visit to the Cleveland Zoo, three years after their treatments began. Both girls are still doing well**

leukemia viruses into which human ADA genes had been spliced. The viruses, which the researchers had rendered harmless by removing all their genes, invaded the T cells and burrowed into their DNA, carrying the ADA gene with them. Finally, a billion or so of Ashi's T cells, many of them now outfitted with a functioning ADA gene, were dripped back into her veins. Four months later, the NIH team performed the same therapy on another ADA-deficient girl, Cindy Cutshall, 9, from Canton, Ohio.

Over the next two years this procedure was repeated a dozen or so times on the little patients. For Ashi it went on until the level of ADA in her bloodstream was 25% of normal, more than enough to protect her. As a precaution mandated by the FDA, she continued to receive weekly doses of PEG-ADA during her gene treatments.

In the past six years, neither girl has had a further infusion of her own altered T cells. Both are taking reduced doses of PEG-ADA, and periodic tests confirm that their re-engineered cells are surviving and producing the ADA enzyme.

Anderson concedes that the historic gene therapy practiced on Ashi did not produce a cure, because the T cells made by her bone marrow still lack their own functional ADA gene. "Nevertheless," he insists, "Ashi does provide the proof of principle that if you put a correct gene into enough cells in a patient, you will correct the disease." ***—By Leon Jaroff***

enabled the therapeutic gene engineered into it to express itself for more than two years.

Wilson expects Phase I trials using AAV to begin later this year, first for the treatment of hemophilia and later for a form of muscular dystrophy, a liver metabolic disease and retinitis pigmentosa, an eye disorder. "It's kind of a new wave," he says.

The other new vector is being fashioned by Salk's Verma. "What we want," he says, "is a virus that is easy to make, that delivers genes at very high efficiency, that can infect a nondividing cell and that enables its therapeutic gene to become part and parcel of the chromosome."

"What we want is a virus that is easy to make and delivers genes at high efficiency."

Seeking the best candidate, Verma zeroed in on the most notorious of the retroviruses—HIV, the virus that causes AIDS. He eliminated the protein envelope that allows the virus entry into T cells, substituted one enabling it to infect a greater variety of cells, and removed the six genes that make the virus dangerous.

Can the lentivirus, as Verma dubbed his creation, ever recombine to generate a virus that has the ability to cause disease? "We have done 115 such preparations," he says reassuringly, "and to date we have never seen a virus that is capable of infecting new cells." Later this year he plans to ask the FDA for permission to begin a Phase I trial for hemophilia.

GENE THERAPISTS ARE LOOKING EVEN FURTHER AHEAD. Pennsylvania's Wilson predicts that the next advance will be a mechanism built into the vector to regulate the expression of a therapeutic gene, turning it on or off. "Most diseases and most drugs require modifying the dose," he explains, "but the genes carried into cells by currently used vectors are either on or off."

This means gene therapy cannot now be used to treat, for example, diabetics. If they were provided with a normal insulin gene that was always turned on, their insulin level would soon be dangerously high. "But the mechanism we have in mind," Wilson says, "will be like a genetic rheostat. The gene will not work until you take a pill, and the more pills you take, the more the gene will be expressed—and if you want to cut off the supply, you simply stop taking the pill."

Some researchers look forward to the day when gene therapy is used to repair damaged genes. With the new vectors, they would infect cells with small molecules that combine DNA and RNA. These hybrid molecules would seek out and bind to the defective gene, enabling it to function normally. "It would be like a repair mechanism," Wilson explains, "rather than a replacement."

French Anderson, ever pushing the envelope, last September asked the National Institutes of Health to begin considering gene therapy in the womb for fetuses found to be afflicted with a hemoglobin deficiency that would kill them before birth and for fetuses with ADA deficiency, the "bubble boy" disorder he treated in his pioneering 1990 trial.

To critics of gene therapy dismayed by what seems to be the slow pace of progress, Anderson urges patience. "People don't understand that the development of an ordinary drug from time of concept to product is 10 years," he says. "We're talking about a revolutionary approach to therapy, and we're only eight years into it."

Floyd Stokes, recovered, vigorous and hard at work on his Texas ranch last week, needs no convincing. "Dr. Isner and these fellows had to do some really far-out thinking to come up with this treatment," he says. "I owe my life to them." ***—With reporting by Alice Park/New York***

There is more to cloning than mere science—and more to human character than scientists can discover in a person's genes

Dolly's False Legacy

By IAN WILMUT

The announcement in February 1997 of the birth of a sheep named Dolly, an exact genetic replica of its mother, sparked a worldwide debate over the moral and medical implications of cloning. Several U.S. states and European countries have banned the cloning of human beings, yet South Korean scientists claimed last month that they had already taken the first step. In the following essay for TIME, *embryologist Wilmut, who led the team that brought Dolly to life at Scotland's Roslin Institute, explains why he believes the debate over cloning people has largely missed the point.*

OVERLOOKED IN THE ARGUMENTS about the morality of artificially reproducing life is the fact that, at present, cloning is a very inefficient procedure. The incidence of death among fetuses and offspring produced by cloning is much higher than it is through natural reproduction—roughly 10 times as high as normal before birth and three times as high after birth in our studies at Roslin. Distressing enough for those working with animals, these failure rates surely render unthinkable the notion of applying such treatment to humans.

SEEING DOUBLE As the author looks on, Dolly gazes at her digitized mirror image in a field near the Roslin Institute

Even if the technique were perfected, however, we must ask ourselves what practical value whole-being cloning might have. What exactly would be the difference between a "cloned" baby and a child born naturally—and why would we want one?

The cloned child would be a genetically identical twin of the original, and thus physically very similar—far more similar than a natural parent and child. Human personality, however, emerges from both the effects of the genes we inherit (nature) and environmental factors (nurture). The two clones would develop distinct personalities, just as twins develop unique identities. And because the copy would often be born in a different family, cloned twins would be less alike in personality than natural identical twins.

Why "copy" people in the first place? Couples unable to have children might choose to have a copy of one of them rather than accept the intrusion of genes from a donor. My wife and I have two children of our own and an adopted child, but I find it helpful to consider what might have happened in my own marriage if a copy of me had been made to overcome infertility. My wife and I met in high school. How would she react to a physical copy of the young man she fell in love with? How would any of us find living with ourselves? Surely the older clone—I, in this case—would believe that he understood how the copy should behave and so be even more likely than the average father to impose expectations upon his child. Above all, how would a teenager cope with looking at me, a balding, aging man, and seeing the physical future ahead of him?

Each of us can imagine hypothetical families created by the introduction of a cloned child—a copy of one partner in a homosexual relationship or of a single parent, for example. What is missing in all this is consideration of what's in the interests of the cloned child. Because there is no form of infertility that could be overcome only by cloning, I do not find these proposals acceptable. My concerns are not on religious grounds or on the basis of a perceived intrinsic ethical principle. Rather, my judgment is that it would be difficult for families created in this way to provide an appropriate environment for the child.

Cloning is also suggested as a means of bringing back a relative, usually a child, killed tragically. Any parent can understand that wish, but it must first be recognized that the copy would be a new baby and not the lost child. Herein lies the difficulty, for the grieving parents are seeking not a new baby but a return of the dead one. Since the original would be fondly remembered as having partic-

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ular talents and interests, would not the parent expect the copy to be the same? It is possible, however, that the copy would develop quite differently. Is it fair to the new child to place it in a family with such unnatural expectations?

What if the lost child was very young? The shorter the life, the fewer the expectations parents might place on the substitute, right? If a baby dies within a few days of birth and there is no reason to think that death was caused by an inherited defect, would it then be acceptable to make a copy? Is it practical to frame legislation that would prevent copying of adults or older children, but allow copying of infants? At what age would a child be too old to be copied in the event of death?

Copying is also suggested as a means by which parents can have the child of their dreams. Couples might choose to have a copy of a film star, baseball player or scientist, depending on their interests. But because personality is only partly the result of genetic inheritance, conflict would be sure to arise if the cloned child failed to develop the same interests as the original. What if the copy of Einstein shows no interest in science? Or the football player turns to acting? Success also depends upon fortune. What of the child who does not live up to the hopes and dreams of the parent simply because of bad luck?

What is missing in all this is consideration of what's in the interests of the cloned child

Every child should be wanted for itself, as an individual. In making a copy of oneself or some famous person, a parent is deliberately specifying the way he or she wishes that child to develop. In recent years, particularly in the U.S., much importance has been placed on the right of individuals to reproduce in ways that they wish. I suggest that there is a greater need to consider the interests of the child and to reject these proposed uses of cloning.

By contrast, human cloning could, in theory, be used to obtain tissues needed to treat disorders such as Parkinson's disease and diabetes. These diseases are associated with cell types that do not repair or replace themselves, but suitable cells will one day be grown in culture. These uses cannot be justified now; nor

are they likely to be in the near future.

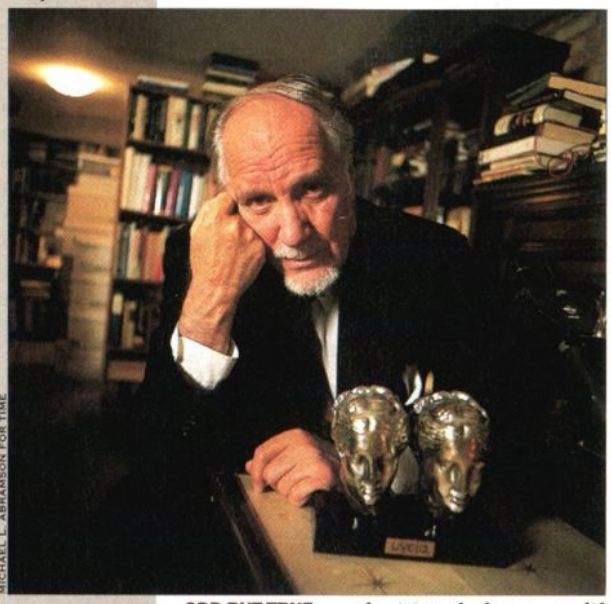
Moreover, there is a lot we do not know about the effects of cloning, especially in terms of aging. As we grow older, changes occur in our cells that reduce the number of times they can reproduce. This clock of age is reset by normal reproduction during the production of sperm and eggs; that is why children of each new generation have a full life span. It is not yet known whether aging is reversed during cloning or if the clone's natural life is shortened by the years its parent has already lived. Then there is the problem of the genetic errors that accumulate in our cells. There are systems to seek out and correct such errors during normal reproduction; it is not known if that can occur during cloning. Research with animals is urgently required to measure the life span and determine the cause of death of animals produced by cloning.

Important questions also remain on the most appropriate means of controlling the development and use of these techniques. It is taken for granted that the production and sale of drugs will be regulated by governments, but this was not always the case. A hundred years ago, the production and sale of drugs in the U.S. was unregulated. Unscrupulous companies took the opportunity to include in their products substances, like cocaine, that were likely to make the patients feel better even if they offered no treatment for the original condition. After public protest, championed by publications such as the *Ladies' Home Journal*, a federal act was passed in 1906. An enforcement agency, known now as the FDA, was established in 1927. An independent body similar to the FDA is now required to assess all the research on cloning.

There is much still to be learned about the biology associated with cloning. The time required for this research, however, will also provide an opportunity for each society to decide how it wishes the technique to be used. At some point in the future, cloning will have much to contribute to human medicine, but we must use it cautiously. ■

Seed of Controversy

Will this unemployed physicist be first to clone humans?



MICHAEL L. ABRAMSON FOR TIME

ODD BUT TRUE Though experts say he's not really credible, Seed has jump-started the debate over human cloning

THE IMMEDIATE RESPONSE TO the birth of Dolly the sheep was a revulsion against the idea of using the same technique to clone human beings. But the news had just the opposite effect on an eccentric scientist named Richard Seed, who declared with an eerie bravado that he was going to produce "half-a-dozen bouncing-baby, happy, smiling clones" before the end of the decade.

Most scientists dismissed his plan as kooky; several U.S. states and 19 European countries outlawed it. But a year later, Seed insists that he is undeterred. He claims to have a partner, an obstetrician-gynecologist, but he won't name him or the three other scientists who he says make up his team. When pressed, he concedes that his colleagues are currently spending no more than 10 hours a week on the project. After all, they have day jobs.

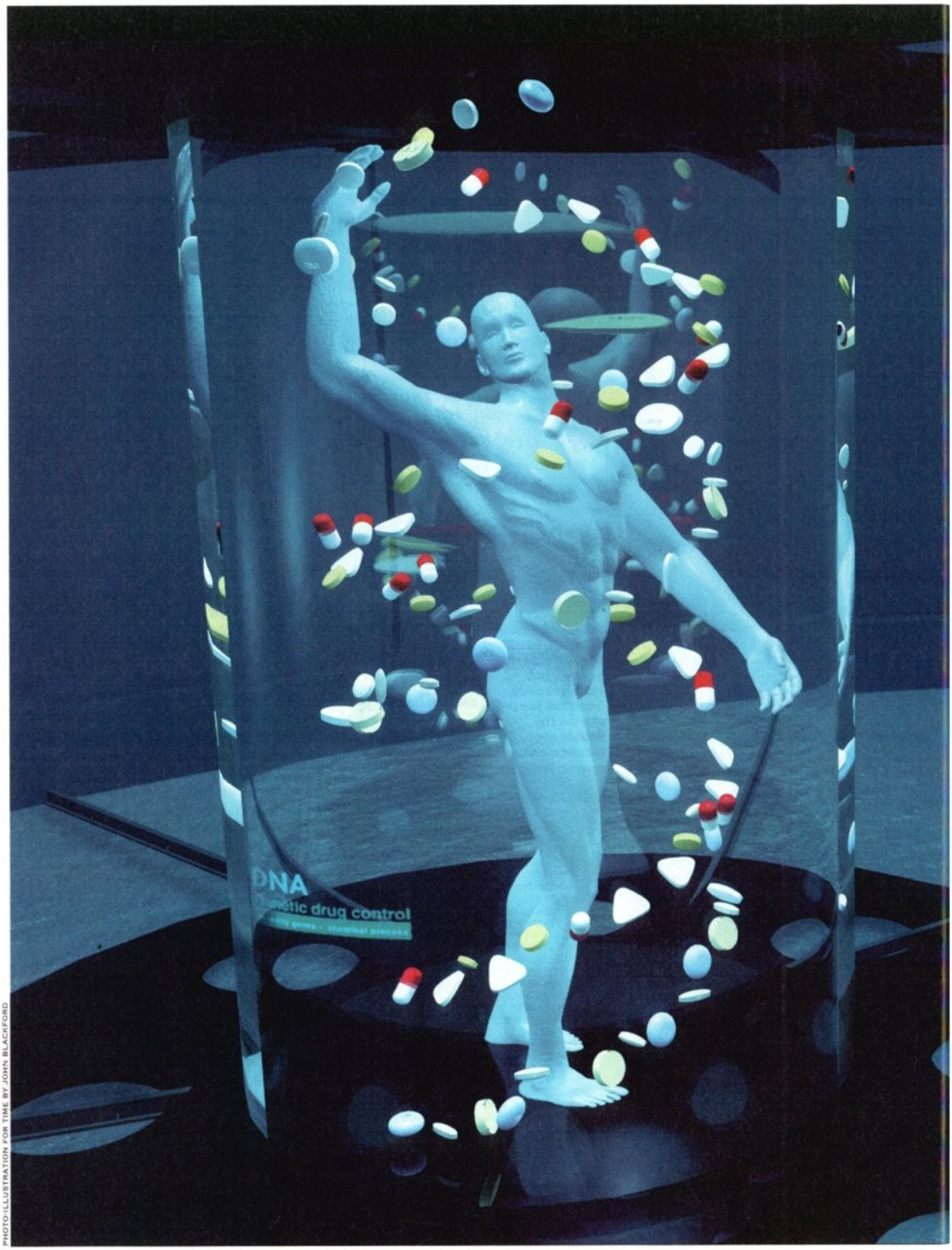
Not so Seed. The unemployed physicist, who has spent a lifetime dabbling in ill-fated ventures, is trying to build support and raise money; he claims to have commitments for $800,000. An impressive start, if true, but still far from the $2.5 million he says is necessary to clone the first human before 2000.

Leaning back in an easy chair in the immaculate Riverside, Ill., bungalow he shares with his wife Gloria, Seed hardly projects the image of a scientific visionary driven to win the cloning race. "I lead a boring life," he says. Indeed, he seems to be spending more time watching television than cloning humans. Lying next to the chair within easy reach is his current reading matter: a textbook called *Principles of Genome Analysis* and the week's TV listings.

His public announcements haven't exactly bolstered his credibility either. First he said he was going to make little baby clones for infertile couples. Then last September—"to defuse criticism that I'm taking advantage of desperate women"—he announced that he would first clone himself. Now he says he will re-create his wife Gloria, an office worker at a FORTUNE 500 company in downtown Chicago. "She's not as excited about it as I am," he says without a hint of irony, "but she's willing to help."

While virtually no mainstream scientist believes Seed will succeed, there has been a subtle shift in attitudes since the bearded, big-boned maverick loomed into view. Seed put into words what many scientists were thinking, and few were surprised to learn last month that a team in South Korea had begun work on human cloning—and even claimed to have produced a four-cell human embryo.

Seed is unconvinced. "The [Korean] results are highly suspect," he says. But he recognizes that the world is not waiting for him. "I'll be devastated if someone else does it first," he says. "But I'll get over it. I'd rather see somebody do it than nobody." That way, at least, Seed could pursue his next project—reprogramming DNA to achieve immortality—which he sees as the all-important successor to cloning. So here's a conundrum: Which would be stranger, a world full of Richard Seeds, or a world in which Seed never goes away? —*By Wendy Cole/Riverside*



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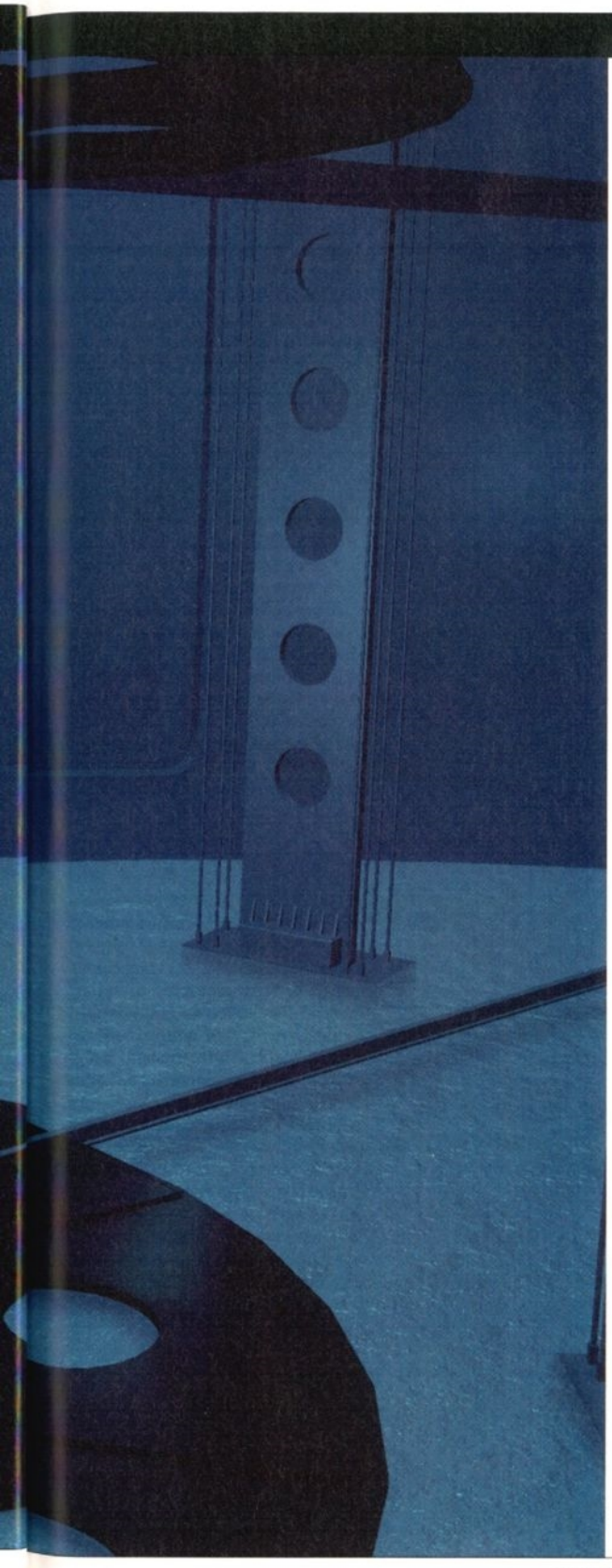


Drugs By Design

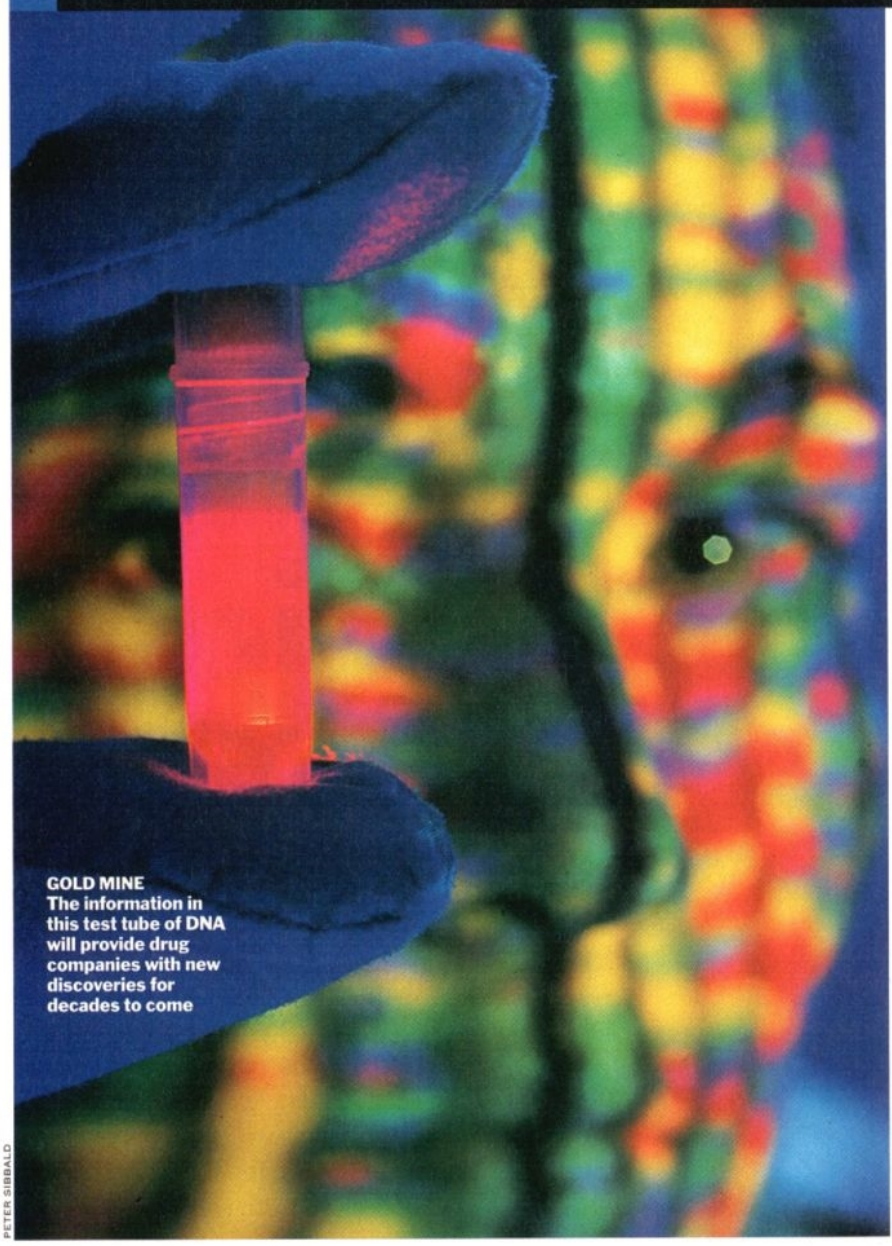
Thanks to genetics, the pharmaceutical industry is exploding with new ideas

By CHRISTINE GORMAN

IT IS THE YEAR 2025, AND SOME THINGS haven't changed. The sky is still blue. The Dow is poised to set another record. And José Rodriguez (Michigan State, class of '04) has just learned that he has colon cancer. But he's not too concerned. Thanks to the genetic revolution that swept over the pharmaceutical industry 30 years earlier, scientists have developed a variety of anticancer drugs that work far better, and with fewer side effects, than the old poison-and-burn treatments of the late 20th century.

The oncologist takes a few cells from José's tumor and places them on a microchip. Within minutes, the chip identifies five mutant genes that, like some kind of diabolical cheerleading squad, have pushed José's cancer to grow, grow, grow. Someday, perhaps soon, doctors will be able to fix the wayward genes themselves. Until then, they will have to rely on the next best thing: drugs developed by pharmaceutical firms that block the destructive messages generated by the errant genes. José's physician selects a combination of treatments that matches the tumor's genetic profile. Six months later, no trace of José's cancerous growth can be found.

That scenario is not as farfetched as it sounds. Talk to anyone in the pharmaceutical industry, and you'll soon discover that genetics is the biggest thing to hit drug research since a penicillium mold floated into Alexander Fleming's petri dish. Sure, scientists



GOLD MINE
The information in this test tube of DNA will provide drug companies with new discoveries for decades to come

PETER SIBBALD

have long known genes play a role in almost every ailment from Alzheimer's to yellow fever. But it is only in the past few years that they've learned how to use that information to identify a multitude of new targets and pathways for drug design. Let's count the ways.

The New Math

Geneticists estimate that there are 2,000 to 5,000 genes that either cause, or predispose humans to, various diseases. In practical terms, that means there will be many, many more potential avenues of research than the entire pharmaceutical industry could possibly hope to investigate over the next 20 years. Each company has a different strategy for exploiting that bonanza, and most are more than happy to tell you what's wrong with the other guy's approach. But they all agree on a few key points:

► Drugs will be safer, more powerful and much more selective than ever before.

► Doctors will be able to consult your genetic profile to determine ahead of time whether you are more likely to respond to one type of medication or another.

► Computers and other digital technologies are going to play a much bigger role in evaluating new research and determining how patients should be treated.

The Good Old Days

To understand how this promising future might come to pass, it pays to review a little history. Back in the old days—which is to say just a few decades ago—the process of discovering a new drug was a lot like shooting a quiver of arrows into the air and then running around to see what they hit. Occasionally scientists would get lucky, as Fleming did in 1928, but most of their efforts were wasted.

The odds started to improve in the 1970s and early '80s as researchers used recombinant-DNA technology to mix and match bits and pieces of hereditary material. Suddenly they had a front-row seat from which to watch genes direct the construction of RNA molecules, which in turn assembled proteins, enzymes and other biological molecules. Instead of shooting their research arrows into the air, drug companies could take aim at defined targets. Focusing on serotonin receptors in the brain, for example, led to the development of Prozac and its chemical cousins for the treatment of depression. Targeting histamine receptors in the stomach produced Tagamet and then Zantac to relieve acid indigestion.

By the 1990s, decades of work had led to the identification of 500 different biological targets for drugs. Thanks to the Human Genome Project, researchers expect to identify another 500 in just the next few years. Soon there will be more new targets than even the largest companies can handle. Then the trick will be to figure out which targets to go after first, and how.

One approach is to focus on the diseases that affect the most people—those associated with aging, say—and to do it by aiming for the targets that are the most accessible. That generally means designing a drug that affects the proteins and enzymes that sit on a cell's surface or in its cytoplasm, not the genes that code for those proteins and enzymes, which are usually tucked away in the protective nucleus of the cell. This is the strategy fa-

vored by such big, traditional drug companies as Merck, Pfizer and Novartis—though it is by no means the only game in town.

Playing with the Big Boys

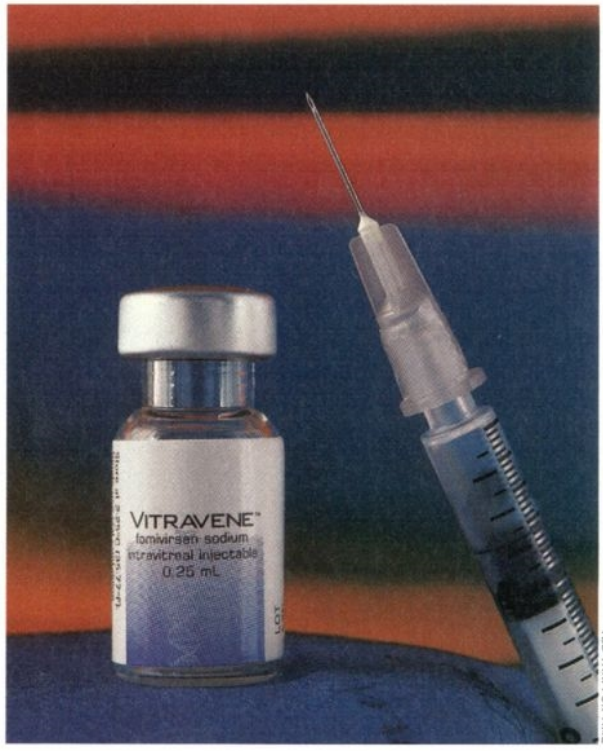
While the pharmaceutical giants are eager to exploit the latest genetic information to create new drugs, they don't see the need to reinvent the wheel completely. The medications they design will still be derived from chemical compounds, or "small molecules" in industry parlance, that happen to be biologically active. (In fact, most of the drugs developed over the past 100 years, from aspirin to Zoloft, are small molecules.) Among the advantages: small molecules aren't destroyed in the stomach, so they can be taken by mouth. Furthermore, they don't get noticed—or attacked—by the immune system. Two of the most active areas of small-molecule research are Alzheimer's disease and cancer.

In 1992 Dr. Allen Roses, then at Duke University and now at Glaxo Wellcome, discovered a link between a particular protein in the blood and the risk of developing Alzheimer's disease. The protein, called apolipoprotein E, works like a cargo ship ferrying cholesterol around the body—a task that seems, at first glance, to have little to do with a degenerative condition in the brain. But 67% of Alzheimer's patients carry a gene that codes for one version of the protein, called apo E4, in contrast to 30% of healthy adults. So although most people with apo E4 never develop Alzheimer's, a significant fraction of them will.

Roses believes he won't have to figure out exactly why apo E4 increases the chances of developing Alzheimer's. As long as he can determine how the brain uses it differently from other versions of the protein, he should be able to develop a drug that either enhances or reduces that effect. The new drug may not be able to treat everyone with Alzheimer's, but at least it could help some.

Finding a likely target, of course, doesn't guarantee success. Consider colon cancer: scientists believe at least three things have to go wrong for colon cancers to form. They liken the situation to a car accident. One of the genes that tells cells to divide (the accelerator) must get stuck in the "on" position. Another gene that tells cells to slow down (the brake) must be disabled. And the molecules that fix any mistakes in the DNA code (the repair crew) have to go on strike. In half of all colon cancers, the accelerator is a gene called *ras*, which makes a protein that stimulates cell growth. It was the ideal target for an anticancer drug.

Or so it seemed. "We banged our heads against the wall for 10 years," says Dr. Alan Oliff, head of cancer research at Merck. "We were on the verge of abandoning the project." Then Oliff's team realized something critical: the *ras* protein can't do its job until it has been activated by another enzyme called a farnesyl transferase. Maybe that would make a better target? Early word is that it does, but Merck won't publish the findings from its first human trials until sometime next year.



TED THAU FOR TIME

SIGHT SAVER
One of the first of a new breed of DNA drugs, Vitravene fights cytomegalovirus, a devastating eye infection in AIDS patients

Building a Better Mousetrap

Whereas traditional drug companies focus on developing chemical compounds, the biotech industry prefers to use biological ones—hormones, proteins and other substances that either already exist in the body or can be created from scratch. Examples include interferon, the clot buster tPA and the new breast-cancer drug Herceptin.

But even among the rarefied biotech élite, there are mavericks who think they have a better idea. They want to move one step closer to the gene by targeting the RNA molecules that transfer information from genes to proteins. And they have the perfect molecular tool with which to do it. By synthesizing strands of DNA that are the mirror image of the RNA they wish to block, researchers can produce a drug that is more specific than anything else on the market. Because it interrupts the "sense" that the cell is trying to make of the RNA molecule, the new technology is called, appropriately enough, anti-sense.

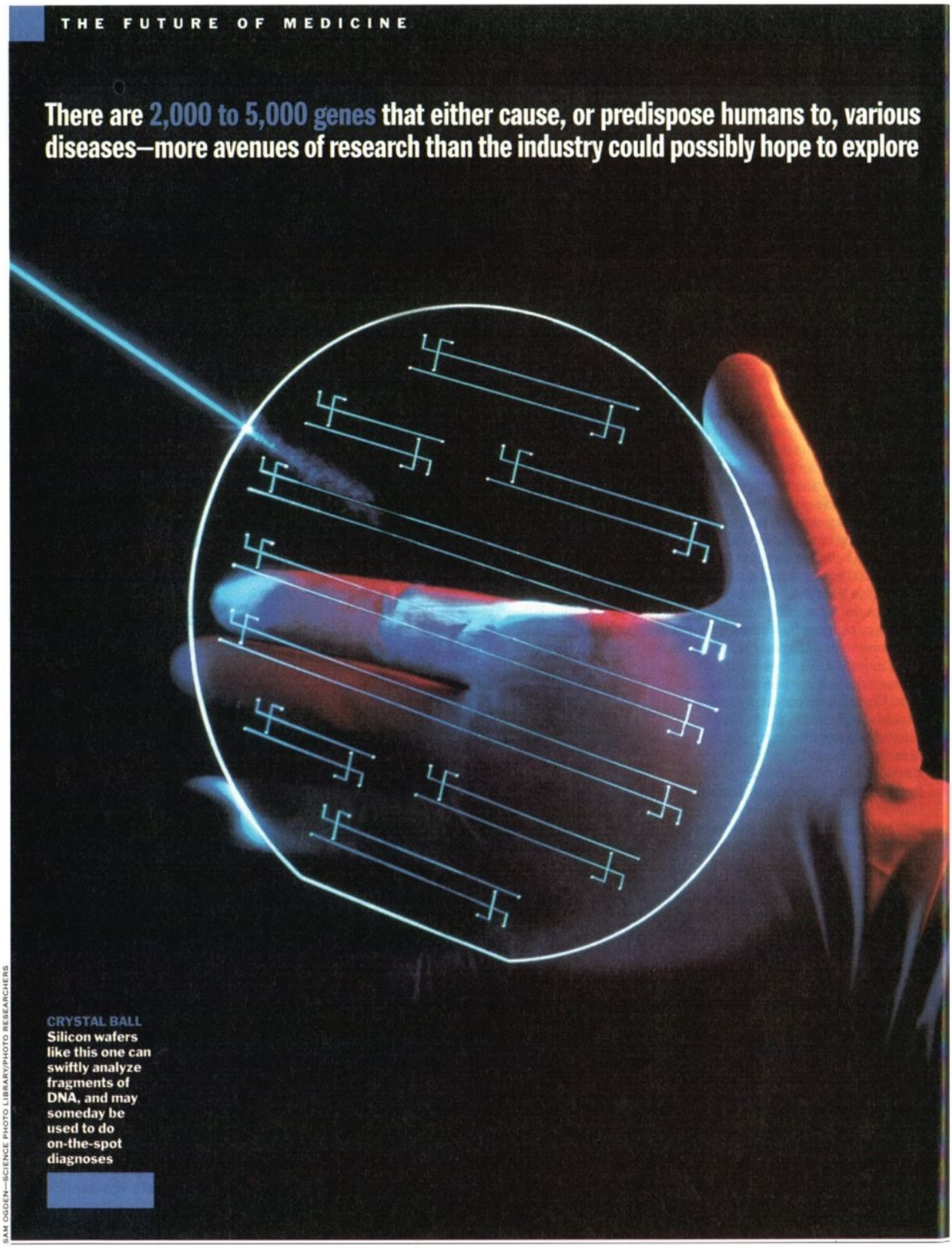
There are still some kinks to work out. For one thing, the body's own immune system often attacks the anti-sense DNA, mistaking it as a potentially harmful virus. For another, many cells in the body don't allow the anti-sense molecules to cross their membranes. "Nine years ago, everyone thought, wow, this is dynamite," says Dr. Art Krieg, editor of the journal *Anti-Sense and Nucleic Acid Drug Development*. "Then they ran into technical hurdles, and the pendulum swung the other way." Now, says Krieg, a few anti-sense compounds are starting to show promise. Among them is a drug called Vitravene, which was approved by the Food and Drug Administration in August and is used to prevent blindness in AIDS patients infected with cytomegalovirus.

Genetic Profiles

Genes don't just tell you how to make drugs. They can also tell you whom to treat.

All drugs have some side effects. By scanning a patient's genetic profile, drug companies may soon be able to figure out ahead of time who is most likely to suffer an adverse reaction. Case in point: Abbott Laboratories has an experimental treatment for asthma that triggers liver abnormalities in about 3% of patients. But it seems to work pretty well in everyone else. So Abbott has asked the French company Genset to see if it can develop a genetic profile of those patients who should never take the medication. The technology isn't foolproof, but it may

There are 2,000 to 5,000 genes that either cause, or predispose humans to, various diseases—more avenues of research than the industry could possibly hope to explore



CRYSTAL BALL
Silicon wafers like this one can swiftly analyze fragments of DNA, and may someday be used to do on-the-spot diagnoses

SAM OGDEN—SCIENCE PHOTO LIBRARY/PHOTO RESEARCHERS

give Abbott the tools with which to market its drug more safely.

Knowing what's in your genes could also take some of the routine guesswork out of medicine. If you're diagnosed with high blood pressure, for example, your doctor may have to try three or four different pills before finding one that works for you. That's because blood pressure is controlled by probably dozens of different genes, any one (or more) of which may be responsible for your particular condition. By screening your DNA and comparing your genetic profile to those of patients who have already responded to particular medications, your doctor may be able to prescribe the right drug the first time around. The money you save would come at the expense of the drug companies, of course, since they would no longer profit from any trial-run prescriptions.

Is There a Computer Scientist in the House?

Focusing on one or two genes and the proteins they code for has already started paying off in the search for new medicines. But the future of drug discovery is going to be centered on a better understanding of complex biological networks like the brain and the immune system. "The only way you can understand complex systems is to look at many genes and proteins at a time," says Lee Hood, chairman of molecular biotechnology at the University of Washington in Seattle. How many? Perhaps 1,000, or 10,000, or even 100,000.

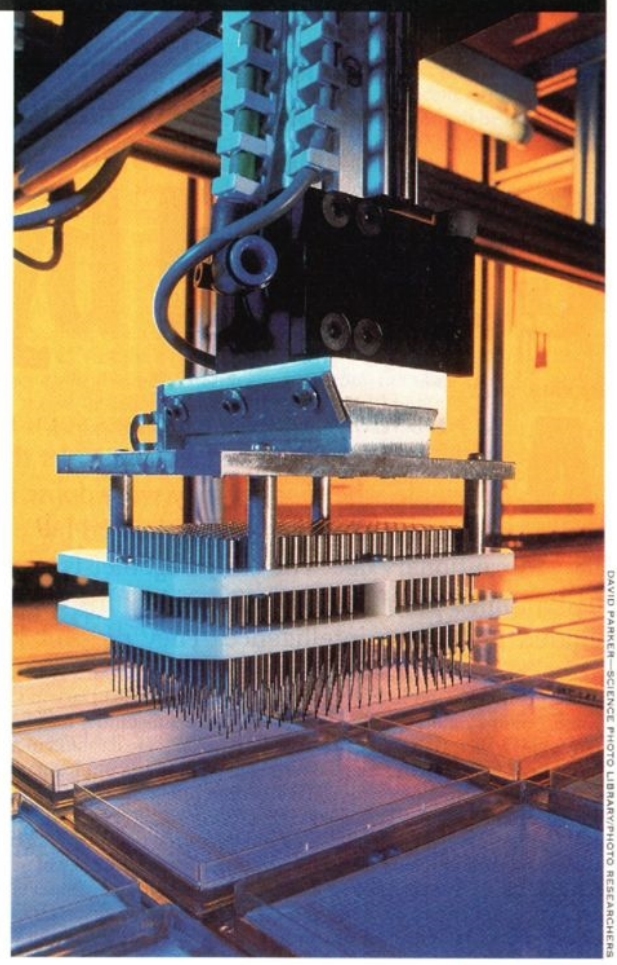
Enter the microchip. Just as chips made of silicon allow computers to process millions of bits of information at a time, chips that process or even incorporate fragments of DNA will one day analyze millions of genetic sequences simultaneously. Patterns that would otherwise take decades to discern could show up in minutes on a gene chip. Doctors will use gene chips to screen their patients for thousands of genetic defects at once. Pharmaceutical researchers will use them to identify which genes are turned on or off in any given disease or system of the body and therefore might make good targets for drug development.

At least that's the theory. Gene chips are so far out on the cutting edge that even many scientists have a hard time believing they'll work. Steve Fodor, CEO of Affymetrix, is used to addressing such doubts. His company, based in Santa Clara, Calif., is widely regarded as the leader in developing gene chips. "We've had to define a lot of new technology, terminology and applications," he says. "But a fantastic new field has sprung up."

So how would you make a gene chip? Let's say you want to identify which genes get turned on, or "expressed," by the immune system in the first few weeks after the AIDS virus begins its attack on the body. First you download the sequences of perhaps 10,000 genes—every A, C, G and T of the hereditary alphabet—into a computer. Then, still using the computer, you figure out what the mirror image of each sequence would be. (DNA can mirror itself as well as RNA.) The aim is to transform the mirror-sequence data into actual strands of DNA that are planted like rows of corn on the glass bed of a chip. Each strand is built up, letter by letter, in much the same way the layers in a silicon chip are created.

Once the strands are complete, the gene chip is ready for use. You take a sample of blood from a patient who has just developed a raging HIV infection. Various genes in his immune system are churning out millions of RNA molecules that will assemble the proteins needed to combat the infection. You extract the RNA and break it into pieces, tag each piece with a fluorescent chemical and pour the whole mess over the gene chip. The RNA tightly binds only to its exact DNA complement on the chip. The fluorescent tag tells you where on the chip you have a match. Then you look up the sequence of each matched spot on the chip and read out a precise catalog of which genes are being expressed. By comparing the results from several patients—some of whom are more successful at fighting the virus than others—you may be able to identify targets that could lead to powerful new anti-AIDS drugs.

Such feats of computational biology are still a few years off or, in the worst case, maybe even a few decades away. The point is, we are just beginning to see how dramatically gene-based science can change the ways in which new drugs are discovered and developed. Blind luck will play an increasingly smaller role as scientists tease out the complex interplay between genes, proteins and the environment. There is going to be confusion—some setbacks and disappointments—at least at first. But most in the field agree that pharmaceutical research has finally entered its golden age. ***—With reporting by Dan Cray/Los Angeles, Bruce Crumley/Paris and Alice Park/New York***



DAVID PARKER—SCIENCE PHOTO LIBRARY/PHOTO RESEARCHERS

AUTOMATION
Pipette-tipped robots are used to map genes and to screen for potential drug targets

WHAT PEOPLE THINK

Since not all prescription drugs work for everyone, would you pay extra for a genetically customized drug that you knew would work for you?

Yes 67%
No 28%

A belief that human intelligence could guide evolution led the world to concentration camps

Cursed by Eugenics

By PAUL GRAY

AT A TIME WHEN SCIENCE PROMISES SUCH DAZZLING ADVANCES IN THE PRACTICE OF MEDICINE, it may be prudent to cast a glance over the shoulder, back to an earlier era when scientists—or people who *thought* they were doing science—stirred hopes that better days were only a generation or so away. The rise and fall of the theory known as eugenics is in every respect a cautionary tale. The early eugenicists were usually well-meaning and progressive types. They had imbibed their Darwin and decided that the process of natural selection would improve if it were guided by human intelligence. They did not know they were shaping a rationale for atrocities.

The man who in 1883 coined the term eugenics, from a Greek stem meaning "good in birth," was a cousin of Charles Darwin's. Englishman Francis Galton (1822-1911) had a substantial inheritance and a Victorian range of scientific curiosity. He dabbled in a number of fields, including geographical exploration, but his passion was mathematics, particularly the infant field of statistics.

In Britain and the U.S., the great age of quantification had begun. An unforeseen consequence of industrialized democracy had been the mammoth increase in the measurement and survey of all sorts of things. Galton relished this new flood of data—"Whenever you can, count" was his motto—and eventually became absorbed in studying the mathematical distribution of what he called "natural ability" among a sample of British subjects. Galton thought natural ability could be tracked down by reading the biographical sketches of eminent Britons in handbooks and dictionaries. When he did so, he discovered that a disproportionate number of these worthies were in some way related to one another. Ergo, he concluded, intelligence and talent were bestowed by heredity. "Could not," he wondered, "the undesirables be got rid of and the desirables multiplied?"

In fairness to Galton, he came to see the encouragement of "good" marriages as a better way to his eugenic heaven than discouraging or preventing "bad" ones. But the seed of a very dangerous notion had nevertheless been sown.

Interest in eugenics grew with the rediscovery and wide dissemination of an obscure Austrian monk's experiments in breeding peas. Gregor Mendel's discovery of genetically transmitted dominant and recessive traits seemed to many the key that would unlock the mysteries of human heredity. In the U.S., biologist Charles Davenport (1866-1944) established, with the help of a $10 million endowment from the Carnegie Institution, a center for research in human evolution at Cold Spring Harbor, N.Y. A strict Mendelian, Davenport believed so-called single-unit genes determined such traits as alcoholism and feeblemindedness. The way to eradicate such failings in the human stock, he argued, was to prevent their carriers from reproducing. He voiced the hope that "human matings could be placed upon the same high plane as that of horse breeding." He declared that prostitution was not caused by poverty but by an "innate eroticism." He advocated eugenic castrations.

In his *In the Name of Eugenics* (1985), an invaluable source for

THE NATIONAL ARCHIVES—CORBIS

everyone interested in this strange movement, historian Daniel J. Kevles notes, somewhat dryly, that "eugenicists identified human worth with the qualities they presumed themselves to possess—the sort that facilitated passage through schools, universities and professional training." Kevles' insight helps explain the almost messianic fervor that eugenicists on both sides of the Atlantic displayed during the early years of this century. These were people who felt themselves and the future of their children threatened. In Britain members of the upper middle class feared they would be swamped and taxed to extinction by the profligate overbreeding of the lower orders. In the U.S., members of the Wasp ascendancy looked with dismay at the flood of immigrants from Southern and Eastern Europe. Italians! Poles! What was the country coming to?

Much of this public fervor looks comically ill informed in hindsight. In the U.S. and Britain, fairs and exhibitions regularly featured exhibits illustrating Mendelian laws of inheritance, often in the form of black-and-white guinea pigs stuffed and mounted to demonstrate the heritability of fur color. Kevles quotes from a chart accompanying such a display: "Unfit human traits such as feeblemindedness, epilepsy, criminality, insanity, alcoholism, pauperism and many others run in families and are inherited in exactly the same way as color in guinea pigs."

Less amusing is the number of intellectuals, businessmen and political leaders who gave eugenics their blessing or fervid support. The list begins with Darwin, who in *The Descent of Man* praised his cousin Galton and decreed that genius "tends to be inherited." Other champions included the young Winston Churchill, George Bernard Shaw, Alexander Graham Bell, John Maynard Keynes, Theodore Roosevelt and the usually taciturn Calvin Coolidge, who declared during his vice presidency that "Nordics deteriorate when mixed with other races."

Eugenics was not just gassy theories. Impressed by the pseudo science, many U.S. states enacted laws requiring the sterilization of those held in custody who were deemed to suffer from hereditary defects. In 1927 the U.S. Supreme Court heard an appeal of Virginia's decision in *Buck v. Bell* to sterilize Carrie Buck, an institutionalized 17-year-old whom the state had decreed a "moral imbecile," the daughter of a "feebleminded" mother and the mother herself of a daughter who was found to be, at age seven months, subnormal in intelligence. The court, by an 8-to-1 vote, rejected Buck's appeal. In his majority opinion, Oliver Wendell Holmes wrote, "The principle that sustains compulsory vaccination is broad enough to cover cutting the Fallopian tubes," and concluded, "Three generations of imbeciles are enough."

Early champions included Winston Churchill, George Bernard Shaw and Teddy Roosevelt

FINAL SOLUTION
Eugenic principles were taken to their horrific conclusion in Nazi Germany, where forced sterilizations gave way to camps like Sachsenhausen

Nowhere, of course, were eugenic theories more enthusiastically codified into binding state doctrine than in Nazi Germany. In 1933 Adolf Hitler's government adopted the Eugenic Sterilization Law. Formulated by the Reich Ministry of the Interior, this edict ordered the compulsory sterilization of all German citizens—not simply those in custody or institutions—who displayed symptoms of a number of presumptively hereditary afflictions, including blindness, schizophrenia and offensive physical deformities. Government officials countered potential objections about the cruelty of this measure by asserting that personal sacrifices would serve the common weal. "We go beyond neighborly love," said one. "We extend it to future generations. Therein lies the high ethical value and justification of the law." As Kevles notes, the Nazis' draconian eugenics program did not originally encompass the anti-Semitism that later so rabidly characterized the Third Reich. But as Hitler and his regime turned ever more fiercely against the Jews, the sterilization of "undesirables" escalated into genocide, a horrifying realization of Francis Galton's vision of the world biologically cleansed according to one group's idea of human improvement.

Eugenics never recovered from the news of what had been carried out under its banner in Hitler's Germany. In truth, a number of people—including G.K. Chesterton, H.L. Mencken, Walter Lippmann and Clarence Darrow—had ridiculed and debunked eugenic theories well before the horrors of the Holocaust occurred and became widely known.

And the flaws, so obvious to us now, in the eugenicists' thinking—starting but by no means ending with their assumption of the immutable heritability of character and the attribution of complex human traits to simple Mendelian genes—did spur, among scientists who recognized the errors, valuable research in the actual science of human genetics. They were wrong, with unintended consequences for millions of people. But the legacy of the eugenicists may be instructive. The next time you hear someone promoting the scientific improvement of the human race, think of them. ■

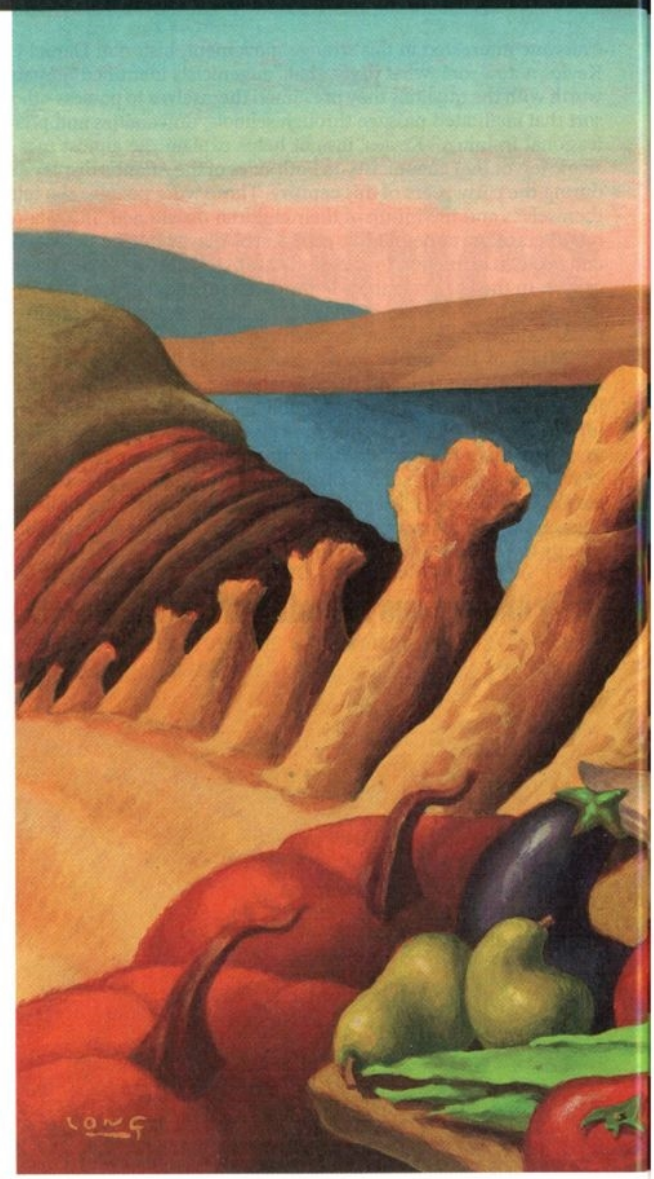
The first commercial products bred by genetic engineering incur a backlash in Europe, where "Frankenstein" fears run deep

Brave New Farm

By **JAMES WALSH** LONDON

You may drive out Nature with a pitchfork, yet she will always hasten back. —Horace, *Epistles*

PITCHFORKS? NOWADAYS WE USE GUNS. A so-called gene gun using gold bullets has become one of the standard methods for rewriting nature's codes. Pellets coated with DNA are fired into the chromosomes of a plant that biotech engineers wish to alter in some amazing way. Then, after patient cultivation to bring out the inserted trait, a prodigy is born. The transformed crop may be corn or cotton with a built-in insecticide, tomatoes that retain their fresh-picked texture on the shelf, or wheat with extra gluten, making for lighter, bouncier bread. The new crop of doctors has been so busy re-enacting the Creation in the past few years that Americans, at least, no longer pay much notice. If genetic engineers had envisioned a quick conquest of the world, however, they have experienced a sharp comeuppance in Europe, where fears about the unknown consequences of "Frankenstein foods" are rampant. So suspicious are Europeans that they are virtually ready to take up pitchforks on behalf of Mother Nature's return.



From a global standpoint Europe's resistance to genetically modified crops is a peculiar case: a complex amalgam of bad timing, conspiracy theories and allegiance to traditions, with perhaps a dash of economic protectionism thrown in. Yet the Continental food fight that continues to pitch up scare headlines in Europe may herald what genetic engineering can expect to encounter as it moves more broadly into pharmaceuticals and medical procedures. It's not just a matter of consumers' smelling something very fishy in the idea of tomatoes given an antifreeze-producing gene from the winter flounder. More broadly, society—at least European society—is beginning to view genetic science as a market-impelled juggernaut out of control and wearing moral blinders.

The notion of science as a Faustian enterprise is deeply embedded in the popular psyche, even in the relatively optimistic U.S. Technologies that tinker with the fundamentals of life can inspire anxieties enough; when increasingly wedded to the profits of Big Business, the exercise can begin to look downright alarming. Author

ILLUSTRATION FOR TIME BY LOREN LONG

Jeremy Rifkin, America's most persistent critic of bioengineering, wonders what is in store for a world in which evolution is treated as a plaything and life as an "invention." A case in point: the announcement in November by Advanced Cell Technology of Worcester, Mass., that it had hybridized human DNA with a cow egg. Says David Magnus, director of graduate studies at the University of Pennsylvania's Bioethics Center: "It's an example of an issue that requires deep, careful thought. Instead, there was a race to get it done as fast as possible, because there were commercial benefits."

That race has produced some truly remarkable things. In one lab researchers are developing food plants fortified with a scrap of DNA that codes for a natural pesticide, eliminating the need to spray clouds of toxin over acres of crops. At another they're developing beans and grains with much higher levels of protein—no small thing for parts of the world where beef and other meats are scarce. At still others they're making potatoes with more starch and less water, coffee beans that grow caffeine-free right on the vine, tomatoes with more solid flesh and less pulp, and strawberries with less natural sugar. Better still, possibly, such *Uber*-plants, passing their clever new traits on to succeeding generations, could yield more bountiful harvests on marginal land in poor, overpopulated countries.

Europe's reticence mixes some good arguments with some ill-informed rhetoric. Does a modified form of wheat grown in France by the Swiss-owned giant Novartis contain a resistance to antibiotics, posing a risk of imparting that resistance to consumers? The company insists the buzz is nonsense, yet a French citizens conference last year solemnly accepted the rumor as fact. Do ge-

WHAT PEOPLE THINK

Should genetically engineered food be labeled as such?

Yes 81% **No** 14%

If food were labeled as genetically engineered, would you buy it for yourself or your family?

Yes 28% **No** 58%

ADRIAN ARBIB—STILL PICTURES

ECO-SABOTAGE
Last November demonstrators uprooted a field of genetically altered plants in Oxfordshire, England

Society is beginning to view genetics as a market-impelled juggernaut out of control

netically altered crops "outbreed" with wild relatives and other plants? Yes, but so do hybrid farm crops produced by classical breeding since time immemorial. The prospect of unwittingly breeding "superweeds" and "superpests" is a justified concern, demanding caution. Yet studies to date suggest herbicide-resistant genes die out in the wild. And when eco-saboteurs raid a test field to uproot plants, as in a highly publicized spectacle on a British farm last July, they seem to be defeating their own calls for further trials of the crops.

AT THE SAME TIME, BIOTECH FIRMS LIKE NOVARTIS, AMERIca's Monsanto and Britain's Zeneca are somewhat disingenuous when they imply that nothing could go wrong with their products. Science has moved at such a dizzying pace that neither politics nor the law, let alone research into unforeseen consequences, can keep up with it. Britain's pre-eminent champion of organic farming, Prince Charles, weighed in on the debate in mid-1998 with a newspaper commentary arguing that transferring genes between utterly unrelated species—fish to tomatoes, for instance—"takes us into realms that belong to God, and to God alone."

What rings the loudest alarm bells, of course, is the specter of cloning humans. No sooner had Dolly the sheep emerged from a Scottish lab than authorities scrambled to build legal pinfolds. Fourteen U.S. states introduced bills to regulate cloning, and President Clinton outlawed the use of federal funds for the purpose—although much of bioengineering has long since slipped that leash. Bioethicist Glenn McGee, Magnus' associate at the University of Pennsylvania, notes that with so much research now financed privately, less and less of it "receives any federal scrutiny."

The difficulty for legislatures lies in striking the right balance, weighing public concerns against the principles of free inquiry and market liberties. In fact, genetic modification is very big business today for the U.S., both domestically and as an export earner. That does not necessarily entail greater dangers than usual, but it can—and does—result in confusion between commercial rights and what properly belongs to the personal or public domain.

While society is torn between benefits and risks, commercial scientists have done a bad job of regulating themselves, in Magnus' view. "Testing with breast-cancer genes was offered far too early," he says. "It wasn't even clear what the tests meant." He adds, "We could literally have had women getting double mastectomies because of a positive result on a genetic test, where in fact the test does not mean that they are at increased risk."

Perhaps because of Europe's deeper suspicions of Big Business, the food fight has prompted a regulatory go-slow on the Continent. One factor is the scare that erupted in 1996 over "mad cow" disease in British beef. Though the disease was caused by feeding animal parts to cows, rather than by genetic meddling, the panic left consumers extremely wary about what goes onto the family dinner table. Herbert Krach of the Swiss Small Farmers Union notes, "For years scientists assured us that feeding animal-based feeds to cattle was harmless." But the cautions also owe something to romantic—and perhaps outdated—notions about agriculture. Says population geneticist Brian Johnson of Britain's conservation watchdog English Nature: "Conventional intensive agriculture has done more damage to wildlife than anything else." Anyone who thinks that pesticide spraying is safer than biotech crops, he says, "must be nuts."

Still, critics contend that consumers should at least have the option of refusing bioengineered foods. The European Union recently introduced mildly restrictive labeling requirements, but no such regime exists in the U.S., Canada or the other countries with rapidly expanding fields of modified crops. Tricky ownership questions also arise: Is a bioengineered potato, or any gene sequence mapped in the lab, a patentable property? These threads are increasingly tightly coiled by nature and science, and not easily unraveled.—***Reported by Helena Bachmann/Geneva, Simon Coss/Brussels, Phil Couvrette/Paris, Nina Planck/London, Ursula Sautter/Bonn and other bureaus***

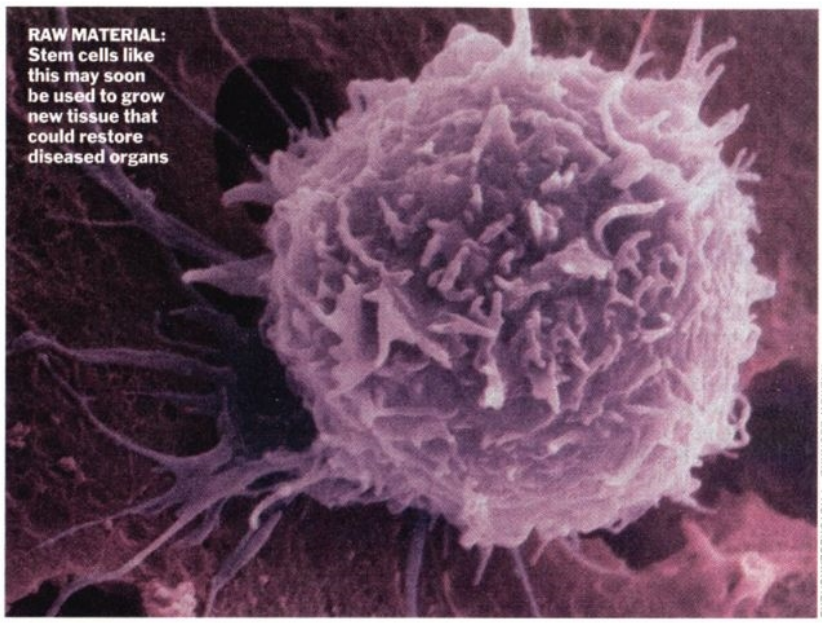
ANTI-CLONER
American critic Jeremy Rifkin protests that evolution is not a toy and life is not an invention to be patented

JEFFREY MARKOWITZ—SYGMA

On the Horizon

Gene therapy and gene-based drugs are two ways we could benefit from our growing mastery of genetic science. But there will be others as well, including new kinds of vaccines, new sources of transplant tissue, even techniques doctors may someday use to stave off the aging process. Here are just a few of the remarkable therapies on the cutting edge of genetic research that could make their way into mainstream medicine in the coming years:

TOMORROW'S TISSUE FACTORY



RAW MATERIAL: Stem cells like this may soon be used to grow new tissue that could restore diseased organs

ANDREW LEONARD—PHOTO RESEARCHERS

WHILE IT'S TRUE THAT JUST about every cell in the body has the instructions to make a complete human, most of those instructions are inactivated, and with good reason: the last thing you want is for your brain cells to start churning out stomach acid or your nose to turn into a kidney. The only time cells truly have the potential to turn into any and all body parts is very early in a pregnancy, when so-called stem cells haven't begun to specialize.

Yet this untapped potential could be a terrific boon to medicine. Most diseases involve the death of healthy cells—brain cells in Alzheimer's, cardiac cells in heart disease, pancreatic cells in diabetes, to name a few. If doctors could isolate stem cells, then direct their growth, they might be able to furnish patients with healthy replacement tissue.

It was incredibly difficult, but last fall scientists at the University of Wisconsin managed to isolate stem cells and get them to grow into neural, gut, muscle and bone cells. The process still can't be controlled, and may have unforeseen limitations. But if efforts to understand and master stem-cell development prove successful, doctors will have a therapeutic tool of incredible power.

The same applies to cloning, which is really just the other side of the coin. True cloning, as first shown with Dolly the sheep two years ago, involves taking a developed cell and reactivating the genome within, resetting its developmental instructions to a pristine state. Once that happens, the rejuvenated cell can develop into a full-fledged animal, genetically identical to its parent.

For agriculture, in which purely physical characteristics like milk production in a cow or low fat in a hog have real market value, biological carbon copies could become routine within a few years. This past year scientists have done for mice and cows what Ian Wilmut did for Dolly, and other creatures are bound to join the cloned menagerie in the coming year.

Human cloning, on the other hand, may be technically feasible but legally and emotionally more difficult. Still, one day it will happen. The ability to reset body cells to a pristine, undeveloped state could give doctors exactly the same advantages they would get from stem cells: the potential to make healthy body tissues of all sorts, and thus to cure disease. That could prove to be a true "miracle cure."

—By Michael D. Lemonick

SPIKING THE POTATOES

WE ALL KNOW THAT EATING FRUITS AND VEGETABLES IS good for us, but within the next decade we could be eating broccoli not just to make Mom happy but also as a way to deliver drugs that stave off infectious diseases or that treat various chronic conditions. "The idea of vaccinating people with edible plants is very new," says Dwayne Kirk of the Boyce Thompson Institute for Plant Research in Ithaca, N.Y. "But it's a lot friendlier than injections."

Because their cells naturally produce large quantities of protein, potatoes and tomatoes seem for now to be the most efficient vehicles for the new approach. Instead of mixing viral or bacterial DNA in a formula for injection, for example, scientists could insert it into soil bacteria. When the bacteria are taken up by the plant, therapeutic DNA material is stitched into the plant's genome. Another method of getting genes into plants is to coat tiny particles of tungsten or gold with foreign DNA, then shoot the particles directly into plant cells. Either way, the plant's cells start to produce whatever proteins the new genes are designed to make. Immunization begins when the plant or its fruit is eaten, prompting the body to churn out the appropriate antibodies.

Plant-based vaccines are particularly attractive for Third World countries, where storage and distribution of drugs are a problem. Eventually, people in these areas may inoculate themselves against diseases simply by growing a crop of genetically engineered fruits or vegetables and eating a few several times a year.

The technique does not have to be limited to infectious diseases, however. It may even be useful for conditions such as Type I diabetes, in which a patient's own immune system destroys essential insulin-producing cells in the pancreas. For diabetics, eating insulin-bearing tubers could eventually train the body's defenses to stop reacting to insulin as if it were a foreign material, all without the bother—or risk—of a needle. *—By Alice Park*

A SHOT FOR AGING BODY PARTS?

EIGHT YEARS AGO, SCIENTISTS DISCOVERED THAT THE TIPS OF chromosomes in tissue cells shorten each time the cells replicate—until a point is reached where the cells stop dividing altogether. That point, called the Hayflick limit, comes after about 50 replications, and may be at the heart of the process we call aging.

Scientists have tried ever since to reactivate the enzyme that lengthens the tips, known as telomeres. Last January they succeeded: Andrea Bodnar and colleagues from the Geron Corp. in Menlo Park, Calif., activated the enzyme telomerase, extended the telomeres and lengthened the life-span of cells in culture by at least 20 divisions past the Hayflick limit. In November, Geron scored another first by reconstituting the telomeres of embryonic stem cells, which are renowned for their ability to turn into any type of cell, making it theoretically possible to rejuvenate parts of any organ with a simple injection.

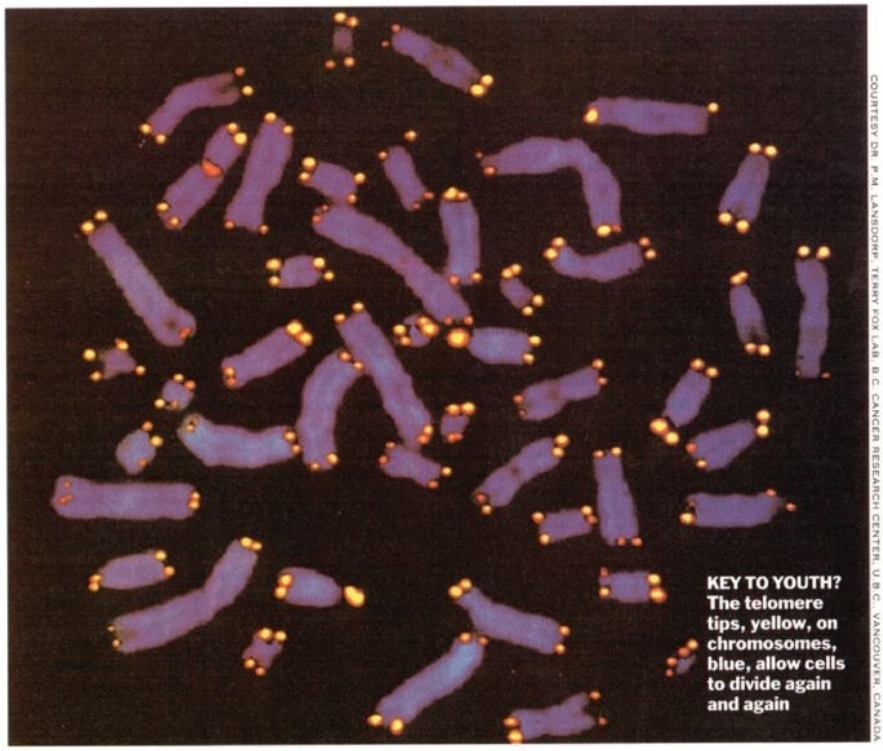
Not everyone is convinced. Leonard Guarente, a specialist on aging from the Massachusetts Institute of Technology, observes that "telomeres seem to be important in getting cells to divide in vitro, but the onus is to show that short telomeres affect aging in vivo. I don't think we know that yet." *—By Clare Thompson*

BEYOND VACCINATION

MOST OF US CAN'T REMEMBER OUR FIRST VACCINATION, but chances are, it was a shot filled with a crippled microbe or perhaps parts of the bug's proteins—just enough to produce a mild infection but not the full-blown disease. Immunizing people against a host of infections in this way has worked reasonably well for more than a century, but geneticists think they can do better.

The vaccines of tomorrow are likely to be far more sophisticated concoctions, made up of snippets of raw DNA from the genome of a virus, bacterium or parasite. Using DNA, as opposed to proteins made by a microbe, elicits a more vigorous, aggressive response from the immune system. While most of the current vaccines do a good job of marshaling antibodies against an invading marauder, they often don't reliably coax the body into churning out killer T cells, the smart bombs of the immune system that strike at the offending microbes with great specificity. In early tests, DNA-based vaccines triggered both responses. For example, immunologists reported last fall that patients injected with an experimental DNA-based malaria vaccine showed not just malaria antibodies but also significant levels of killer T cells.

The potential goes beyond bugs. Because gene-based vaccines can easily be manipulated by adding or deleting DNA, doctors are applying the technique to treat various forms of cancer. The work is still limited to animals, but researchers have developed inoculations made up of tumor cells that act as a red flag to rally an animal's immune system against the tumor. "There is a long road ahead" for these cancer vaccines, says Duke University's Dr. Eli Gilboa. "But it's very promising." *—A.P.*



KEY TO YOUTH? The telomere tips, yellow, on chromosomes, blue, allow cells to divide again and again

COURTESY DR. P.M. LANSDORP, TERRY FOX LAB, B.C. CANCER RESEARCH CENTER, U.B.C. VANCOUVER, CANADA

All for the Good

Why genetic engineering must soldier on

By JAMES D. WATSON

THE PIONEERS: Watson, left, and Crick pose with a model of DNA in 1953, shortly after deducing its structure

CORBIS-BETTMANN

THERE IS LOTS OF ZIP IN DNA-based biology today. With each passing year it incorporates an ever increasing fraction of the life sciences, ranging from single-cell organisms, like bacteria and yeast, to the complexities of the human brain. All this wonderful biological frenzy was unimaginable when I first entered the world of genetics. In 1948, biology was an all too descriptive discipline near the bottom of science's totem pole, with physics at its top. By then Einstein's turn-of-the-century ideas about the interconversion of matter and energy had been transformed into the powers of the atom. If not held in check, the weapons they made possible might well destroy the very fabric of civilized human life. So physicists of the late 1940s were simultaneously revered for making atoms relevant to society and feared for what their toys could do if they were to fall into the hands of evil.

Such ambivalent feelings are now widely held toward biology. The double-helical structure of DNA, initially admired for its intellectual simplicity, today represents to many a double-edged sword that can be used for evil as well as good. No sooner had scientists at Stanford University in 1973 begun rearranging DNA molecules in test tubes (and, equally important, reinserting the novel DNA segments back into living cells) than critics began likening these "recombinant" DNA procedures to the physicist's power to break apart atoms. Might not some of the test-tube-rearranged DNA molecules impart to their host cells disease-causing capacities that, like nuclear weapons, are capable of seriously disrupting human civilization? Soon there were cries from both scientists and nonscientists that such research might best be ruled by stringent regulations—if not laws.

As a result, several years were to pass before the full power of recombinant-DNA technology got into the hands of working scientists, who by then were itching to explore previously unattainable secrets of life. Happily, the proposals to control recombinant-DNA research through legislation never got close to enactment. And when anti-DNA doomsday scenarios failed to materialize, even the modestly restrictive governmental regulations began to wither away. In retrospect, recombinant-DNA may rank as the safest revolutionary technology ever developed. To my knowledge, not one fatality, much less illness, has been caused by a genetically manipulated organism.

The moral I draw from this painful episode is this: Never postpone experiments that have clearly defined future benefits for fear of dangers that can't be quantified. Though it may sound at first uncaring, we can react rationally only to real (as opposed to hypothetical) risks. Yet for several years we postponed important experiments on the genetic basis of cancer, for example, because we took much too seriously spurious arguments that the genes at the root of human cancer might themselves be dangerous to work with.

Though most forms of DNA manipulation are now effectively unregulated, one important potential goal remains blocked. Experiments aimed at learning how to insert functional genetic material into human germ cells—sperm and eggs—remain off limits to most of the world's scientists. No governmental body wants to take responsibility for initiating steps that might help redirect the course of future human evolution. These decisions reflect widespread concerns that we, as humans, may not have the wisdom to modify the most precious of all human treasures—our chromosomal "instruction books." Dare we be entrusted with improving upon the results of the several million years of Darwinian natural selection? Are human germ cells Rubicons that geneticists may never cross?

Unlike many of my peers, I'm reluctant to accept such reasoning, again using the argument that you should never put off doing something useful for fear of evil that may never arrive. The first germ-line gene manipulations are unlikely to be attempted for frivolous reasons. Nor does the state of today's science provide the knowledge that would be needed to generate "superpersons" whose far-ranging talents would make those who are genetically unmodified feel redundant and unwanted. Such creations will remain denizens of science fiction, not the real world, far into the future. When they are finally attempted, germ-line genetic manipulations will probably be done to change a death sentence into a life verdict—by creating children who are resistant to a deadly virus, for example, much the way we can already protect plants from viruses by inserting antiviral DNA segments into their genomes.

If appropriate go-ahead signals come, the first resulting gene-bettered children will in no sense threaten human civilization. They will be seen as special only by those in their immediate circles, and are likely to pass as unnoticed in later life as the now grownup "test-tube baby" Louise Brown does today. If they grow up healthily gene-bettered, more such children will follow, and they and those whose lives are enriched by their existence will rejoice that science has again improved human life. If, however, the added genetic material fails to work, better procedures must be developed before more couples commit their psyches toward such inherently unsettling pathways to producing healthy children.

Moving forward will not be for the faint of heart. But if the next century witnesses failure, let it be because our science is not yet up to the job, not because we don't have the courage to make less random the sometimes most unfair courses of human evolution. ■

James Watson and Francis Crick won a Nobel Prize for Medicine for their 1953 discovery of the structure of DNA. Watson was the first director of the Human Genome Project; he now serves as president of Cold Spring Harbor Laboratory

FOX GETS SUPER

Don't have a cow, man, but the network that Bart Simpson has called home for the past nine years is now betting its future on three new cartoon series

By MICHAEL KRANTZ

IN THE PILOT EPISODE OF THE FOX network's new animated sitcom *The PJs*, Thurgood Orenthal ("Goody") Stubbs, the superintendent of an inner-city housing project, tries to chase a swarm of vagrants out of his embattled building. "Well, I'd love to stay and chat," says one, a series regular named Smokey, "but crack don't smoke itself."

Is this the future of network television? Fox is sure hoping it is. One of the few breakout shows last year was Comedy Central's scabrous *South Park*, and the year before, Fox had its own success with that animated paean to redneck Texas, *King of the Hill*. Now the genre that seems to offer the quickest shortcut to countercultural chic is becoming more popular than ever. The three start-up networks (Fox, UPN and the WB) have scheduled seven new prime-time cartoon series for this year, and more are in the works. "Animated shows stand out from the pack," says Tony Krantz, CEO of Imagine Television, one of the producers of *The PJs*. "They look extraordinary, and the brand of humor can be quite striking."

No one is showing more gusto than Bart Simpson's home network. Between now and March, Fox will launch three high-profile animated sitcoms: *The PJs*, newcomer Seth MacFarlane's *Family Guy*, and the long-awaited *Futurama*, from *Simpsons* creator Matt Groening. "People expect us to be different," says Mike Darnell, the wire-haired programming impresario responsible for Fox's "shockumentaries" (*World's Deadliest Swarms, When Good Pets Go Bad*). "They can find live-action sitcoms everywhere else. They don't have to come here for them."

The problem for Fox is that viewers haven't been coming for much at all. The fall season was a disaster for the network,

FAMILY GUY
The 25-year-old wunderkind Seth MacFarlane offers his wry take on the average American dysfunctional family.

FOX

ANIMATED

which swiftly shelved three of its five new series. Only *That '70s Show* and *Brimstone* have a shot at renewal. That dismal record cost entertainment president Peter Roth his job. Doug Herzog, the executive who brought the *South Park* gang to Comedy Central, was named his replacement in November but is only just now taking the reins.

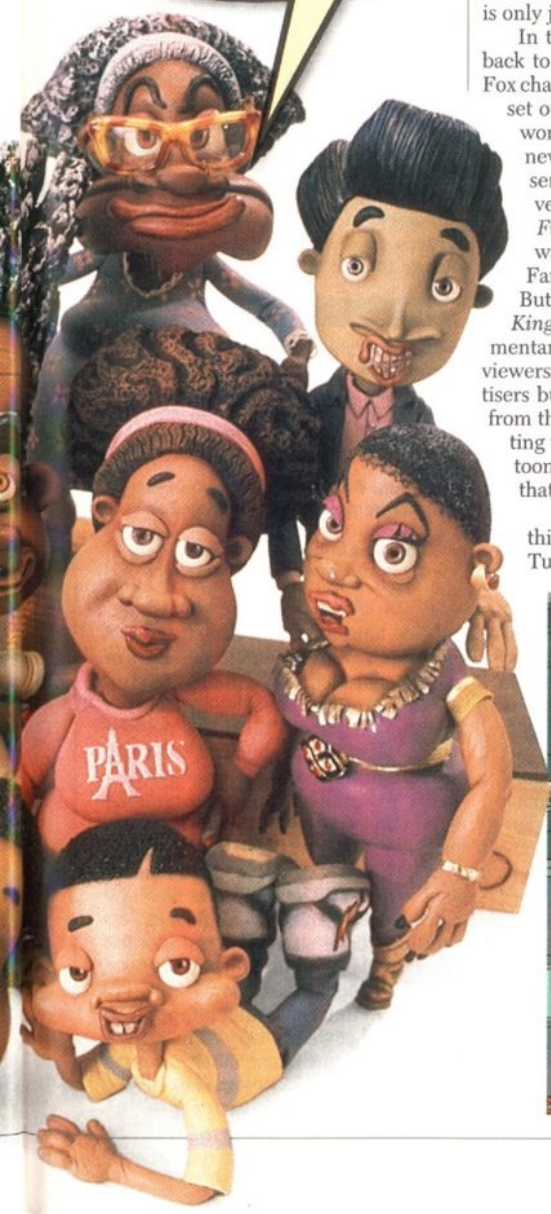
In the interim Fox has literally gone back to the drawing board. Darnell and Fox chairman David Hill insist they didn't set out to become the Animation Network, that the confluence of three new cartoon programs is sheer serendipity. Groening has been developing the millennium-timed *Futurama* for years, and *The PJs* was signed up months before MacFarlane arrived with *Family Guy*. But it's also true that *The Simpsons, King of the Hill* and Darnell's shockumentaries score best with young male viewers, who are much coveted by advertisers but increasingly hard to tear away from their Sony PlayStations. Fox is betting that an even more aggressive cartoon slate will increase its appeal to that demographic mother lode.

First out of the blocks (it debuts this Sunday before settling in on Tuesday night following *King of the Hill*) is *The PJs* (shorthand for "the projects"), the brainchild of Eddie Murphy and perhaps the riskiest of Fox's new cartoon ventures. Murphy sold Imagine on his idea two years ago. The result is a visual tour de force. The puppeteers of the Will Vinton Studios, best known for the California Raisins, have created a colorful 3-D universe of intricately animated clay figures expressive enough to almost pop off the screen. Making sure they land in viewers' hearts is the mission of a writing staff led by executive producers Larry Wilmore and Steve Tompkins (two former stand-ups who met while writing for *In Living Color*). They've made Goody, voiced by Murphy, a gruff but endearing tour guide through a community of eccentric black and Latino characters. Their stories, from the attempted rehabilitation of a local porn theater to Goody's battle to save his beloved new front door from the ravages of spray-paint-wielding gangbangers, take a warmhearted but hard-eyed look at contemporary urban life. The show looks gorgeous. The milieu is fresh. The scripts are funny. Oh, and did we mention Eddie Murphy?

Yet *The PJs* isn't even the hottest new show on Fox's January animation schedule. The honor of debuting in the post–Super Bowl slot goes to *Family Guy*, the creation of Seth MacFarlane, a hitherto unknown artist who was just a year out of the Rhode Island School of Design when

JIM LOMMASSON—FOX

THE PJS
Eddie Murphy provided the original idea and one of the voices for this show about the residents of an inner-city housing project



FUTURAMA
A decade after launching *The Simpsons*, Matt Groening leaps forward into "New New York" in the year 3000

FOX

Fox shrewdly plucked him from the Hanna-Barbera animation stables. "Stunningly clever" is the way Darnell describes MacFarlane's initial pitch, at which the wunderkind performed all the voices himself. "Two weeks later we ordered 13 episodes, and Seth became a star," says Darnell. A seven-minute presentation reel the network took to last May's "up-front" screenings for advertisers, he adds, "was far and away the funniest thing we showed."

Network executives are supposed to say things like that, but an early 50-page script for the *Family Guy* pilot makes it clear that MacFarlane, at just 25, is a prodigiously talented writer. *Family Guy*, which is set in a sleepy Rhode Island city, falls squarely within the medium's venerable archetype of familial dysfunction, which is to say that Mom, Lois, is a saint; Dad, Peter, is a boob; the kids are mutants (baby Stewie, for instance, is an evil genius plotting world domination); and the voice of reason is Brian, the family's talking dog. The early plots are standard-issue situation comedy (Dad gets laid off, Mom mounts a chaotic production of *The King and I*), but in the pilot script, at least, MacFarlane's pell-mell wit recalls *The Simpsons*' fevered early-'90s creative peak. Punch lines spill out furiously as the show spirals into multilayered flashbacks and inventive fantasies (when Peter wonders whether to lie to his wife, for instance, the angel and the devil that duel cunningly over his shoulders turn out to have angels and devils dueling over theirs).

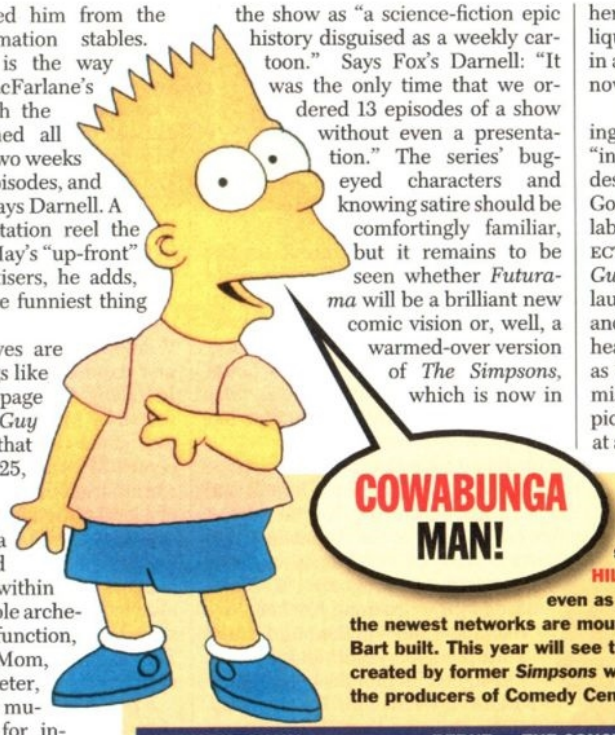
Still, the most anticipated of Fox's new trinity may be Groening's *Futurama*, now scheduled to arrive in March. Fox has waited 10 years for a new show from the *Simpsons* auteur. Here's the pitch: on New Year's Eve 1999, a pizza-delivery guy named Fry falls into a cryogenics vat. He defrosts 1,000 years later in "New New York," befriends an alcoholic robot named Bender and a one-eyed cyclops chick named Leela, and resumes semi-gainful employment at Planet Express, delivering packages throughout the galaxy.

We'll buy that. Groening describes the show as "a science-fiction epic history disguised as a weekly cartoon." Says Fox's Darnell: "It was the only time that we ordered 13 episodes of a show without even a presentation." The series' bug-eyed characters and knowing satire should be comfortingly familiar, but it remains to be seen whether *Futurama* will be a brilliant new comic vision or, well, a warmed-over version of *The Simpsons*, which is now in its 10th season and still going strong.

That kind of longevity won't be easy for the newcomers to achieve. Once a novelty, the animation genre is at risk for oversaturation. The briefly mighty *King of the Hill* saw its ratings plummet when Fox moved it from its cushy post-*Simpsons* berth. *The PJs* in particular could be a tough sell to a public conditioned to the white-bread worlds of *The Simpsons* and *King of the Hill*. Last week a New York *Times* article delineated network programming's increasing racial stratification—*ER* and *Friends* vs. the Steve Harvey and Jamie Foxx shows. Will whites respond to *The PJs*' gritty inner-city vision? For that matter, will blacks and Hispanics embrace a show whose regulars include the voodoo-obsessed Haiti Lady, a homeless crackhead named Smokey and, in Goody, a hero who is rarely without a trusty malt liquor "40" in hand? *The PJs* is "high risk in all ways," admits Darnell. "But it's innovative and interesting."

It's a measure of the networks' growing desperation that they suddenly find "innovative" and "interesting" to be so desirable. A typical *PJs* moment shows Goody approaching a forbidding fortress labeled HUD: KEEPING YOU IN THE PROJECTS SINCE 1963. And while the *Family Guy* pilot offers the sort of traditional laugh-track lines that lifted Tim Allen and (soon) Ray Romano into syndication heaven ("I am the man of this house, and as the man I order you to give me permission to go to this party"), it also depicts a scrawny Hitler in a gym seething at a buff rabbi, surrounded by hot babes, and God himself sitting shamefaced in a pew while a minister details his abuse of Job. "Whoa! Is that really the blood of Christ?" asks Peter after sipping from the Communion goblet. "Yes," says the reverend. "Man!" Peter exclaims. "That guy musta been wasted 24 hours a day!"

Put material like this in a live-action sitcom, and you've got the quickly canceled likes of UPN's slave-era would-be satire *The Secret Diary of Desmond Pfeiffer*. But as *The Simpsons* has long since proved, the cartoon format lets you slip some piquant zingers under the cultural radar. "Eddie Murphy's central reason for doing this show," says *PJs* producer Wilmore, "is that puppets can say things that we can't say." This spring Fox will learn just how much America wants to hear. —*With reporting by Jeanne McDowell/Los Angeles*



Can Fox keep the cartoon crown? THE SIMPSONS is still going strong, but ratings for KING OF THE HILL are way down from last year, and even as Fox restocks its animation arsenal, the newest networks are mounting attacks on the house that Bart built. This year will see the debut of rival prime-time sitoons created by former *Simpsons* writers (THE DOWNTOWNERS) and the producers of Comedy Central's *Dr. Katz* (HOME MOVIES).

NETWORK	SHOW	DEBUT	THE CONCEPT
UPN	Dilbert	Jan. 25	The comic-strip Everyman (voiced by Daniel Stern) deals with the usual corporate madness
	Home Movies	April	Wacky world of an eight-year-old budding auteur and his divorcé mom (Paula Poundstone)
The WB	Baby Blues	This fall	The comics, again: first-time parents Darryl and Wanda MacPherson cope with baby Zoe
	The Downtowners	This fall	Four offbeat roomies in a big-city loft live it up with assorted colorful friends and neighbors

Sounding the Waters

PBS explores the music along the Mississippi

By CHRISTOPHER JOHN FARLEY

THIS ISN'T MTV. THIS ISN'T TOP-40 RADIO or the *Billboard* Hot 100 singles chart. These are two street performers named David and Roselyn, playing songs for spare change in the French Quarter of New Orleans. This is Sylvester ("Sunshine") Lee teaching a class in African drumming in East St. Louis, Ill. This is polka accordionist Karl Hartwich and Cajun bandleader D.L. Menard and bluesmen Big Jack Johnson and Little Milton.

They are the stars of *River of Song: A Musical Journey down the Mississippi*, an ambitious four-hour, four-part documentary series that begins airing on PBS stations this month (check local listings). The series, written by Elijah Wald, a music critic for the Boston *Globe*, and directed by Boston-based filmmaker John Junkerman, is a multimedia event: there's a corresponding seven-hour, seven-part series airing on Public Radio International; a 36-song, two-CD sound track (Smithsonian Folkways); and a 352-page companion book (St. Martin's). But the purpose of each is singularly focused: to document the contemporary musical traditions that thrive on the banks of the Mississippi, from Lake Itasca, the river's source, to where the waters empty into the Gulf of Mexico.

River of Song isn't documentary broccoli. The viewer isn't assailed with dates and events, fussy terminology and black-and-white daguerreotypes with accompanying narration by overly earnest Hollywood actors. The story is told through a series of punchy personal portraits of the musicians who live in the cities and towns along the Mississippi, places like Davenport, Iowa, and Festus, Mo. We get to know these musicians not as representatives of trends and genres but as regular folks trying to make a living and a little music as well. We see them sweating through performances, straightening their hair with hot combs in their kitchens, jamming with their friends in their living rooms.

The series is nimbly narrated by folk-punk guitarist Ani DiFranco, who brings curiosity and energy to the project. "Beneath the surface of mainstream popular culture, there is the ever-present undercurrent of organically generated music," DiFranco writes in the *River of Song* companion book. "I'm talking about the indigenous, unhomogenized, uncalculated sound of a culture becoming itself in the streets, bars, gyms, churches and back porches of the real world."

The musicians here are generally not superstars, although such nationally known acts as Soul Asylum and the Mississippi Mass Choir do make appearances. And a few of the performers featured deserve a shot on Leno or Conan O'Brien, chief among them the spirited New Orleans hip-hop brass band Soul Rebels. Most of the acts on *River of Song*, however, seem content with local renown. They display a commitment that's deeper than celebrity: for them, music isn't simply a means to acquire wealth or fame; it's a method of preserving traditions and a way of life. "We, the young generation, are the glue that keeps the culture going," says Geno Delafose, a Creole Zydeco musician who appears in the series. "If we don't continue playing the music, then it's gonna be lost."

The series' final scene is its saddest and wisest. On Delacroix Island, at the mouth of the Mississippi, we meet Irvan and Allen Perez, two cousins who belong to the Isleños, a Spanish-speaking people who first settled in Louisiana 200 years ago. The Perezes are fishermen. As they work, they sing slow, bittersweet a cappella songs called *décimas*—10-stanza numbers, mostly in Spanish, that tell the stories of their lives and communities. They sing of shrimp boats and muskrat trappers, bad weather and home mortgages. Their voices are piercing and pure. Allen sings:

"Encontre el trampero esta, el mosque y el agua alta."

(Against this trapper are mosquitoes and high water.)

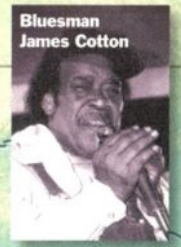
"Y para acabar completa, la banca le manda carta ..."

(And to finish him completely, the bank sent him a letter ...)

It's a mournful song but stubbornly hopeful. His performance reminds the listener that American music is broad and big, like a river, and it keeps flowing. Pop music suddenly seems like just a glass of tap water. Allen's song is one you'll probably never hear on the radio, never see performed on TV—except on *River of Song*. How much other water is unexplored? Tune in to this series and drink deep. ■


Punk rockers Babes in Toyland


African drummer Sylvester ("Sunshine") Lee


Bluesman James Cotton


Cajun fiddler Leo Abshire

MAP BY ED GABEL; PHOTOS BY THEO PELLETIER

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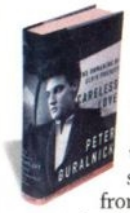
The Fall of The King

Volume II of Peter Guralnick's masterly telling of Elvis' life

By JAY COCKS



THERE IS A RED LIGHT RIGHT at the start. In 1994's *Last Train to Memphis: The Rise of Elvis Presley*, Peter Guralnick movingly, and with the greatest empathy, showed the unlikely and glorious shaping of a poor white boy from the Deep South into a musical demigod. *Careless Love: The Unmaking of Elvis Presley* (Little, Brown; 767 pages; $27.95), the second and concluding volume, is a long coast on the dark downside, a story of ugliness and indulgence and encroaching desperation.

"It is, I think, a tragedy, and no more the occasion for retrospective moral judgments than any other biographical canvas should be," Guralnick writes, switching quickly from slowdown to full stop. "I know of no sadder story." Any of the black bluesmen Guralnick loves and writes about so well could tell him a dozen before a dropped dime hit the floor. But no bluesman, and few entertainers of any kind, has managed to achieve the sheer dimension of Presley's story. Just as Elvis' girth fascinated fans and the press during his last, misbegotten years, so too it is the outsize scale of Presley's life that makes the story irresistible. Or, at least, unavoidable. The King, dying on the shag-carpeted bathroom floor of Graceland, his gold pajama bottoms around his ankles, his face in a puddle of vomit, was so overindulged and tuned out of reality that he must have been surprised to discover he was mortal.

He was a junkie, mostly by prescription; a hedonist, generally by inclination; and a profligate, largely by longing. He wanted to be the naughty boy and the good son both. He carried his collection of police badges with him everywhere, a putative peace officer who loved to disturb the peace. He was afraid of the dark, so he slept in the day, explaining, "I know in the daytime when I go to sleep that it's dark in my room, and I pretend like it's night, but I know it's daytime, and I'm not afraid to fall asleep."

DON CRAVENS—LIFE

1958 With his father Vernon and mother Gladys, whose death that year he never fully got over

WHITE HOUSE PHOTO—AP

1970 His offer to work in President Nixon's antidrug war didn't stop his own abuse of prescription pills

GENE SPATZ—SYGMA

1977 By the year of his death, he was still performing, but had become bloated almost beyond recognition

Whatever he did with his women—have a calculator handy to keep count and a schematic to keep track—he retained a kind of adamant adolescence, fearful and aggressive at once. In bed he preferred kissing, snuggling and cuddling to getting down to the serious business of physical intimacy; or, in the indelible words of one of his girlfriends, Sheila Ryan, "he preferred pumping to actual sex." If the affair progressed, Ryan observed, "all of a sudden you graduated into Mother. You were expected to take care of him ... He needed water, he needed pills, he needed Jell-O, he needed to be read to." But however long they lasted, these women never passed caretaker status. He could give his whole heart only to his real mother Gladys, whose death closed the first volume, as her son went off for his hitch in the Army.

Elvis remained haunted by Gladys to the end of his days. He may have been prodigious, but, in Guralnick's thorough and compassionate telling, he could never be the prodigal son. He paid regular visits to her grave, as if trying to reclaim something. He traveled around the country, but he never left home in any deep sense. Indeed, at the end, he hardly left his room. "Oh, God, son, please don't go, please don't die," his father Vernon wailed as Elvis' daughter Lisa Marie, 9, ran frantically around the house, trying to get into the bathroom where her father lay dead, yelling, "Something's wrong with my daddy, and I'm going to find out."

Maybe what was wrong was the music. Simple as that. Because Presley, in the proudest sense, was a simple man, and the music was always his glory, his animating spirit, his means, even at his bleary end, of temporary transcendence. And the music had been compromised, so stunted that his soul just shut down. Maybe part of his heart died when Gladys passed, or maybe he just lost heart. But his life also started to drift as the music spun out of control. His manager, Colonel Tom Parker, had wrapped him so tight in a skein of interwoven business and publishing deals that he had little creative room to move. "We're caught in a trap," he sings with devastating intensity in *Suspicious Minds*, one of the great tunes of the later years, sounding like a lifer who has the keys to his own cell but has lost them somewhere in the dark that frightens him so.

In the end, of course, the dark overwhelmed him. *Careless Love*, a chronicle of shadows and sadness, is no sentimental epitaph. It is the fine and careful measure of a pilgrim traveler who was never sure what he wanted, gave too much of what he got, and had to say Amen before he could even be sure the Lord was listening. ■

Full Terms of Endearment

A daughter comes of age. And a mother does too

THE LOVE BETWEEN MOTHERS AND daughters can weather a thousand tiny betrayals. What teenage girl has not grimaced, on occasion, at the spectacle of her mother's perceived inadequacies? And that contempt can flow easily, prompted by no more than a gesture of unwanted maternal affection. Nor are mothers above sin, particularly when their daughters threaten to surpass them.

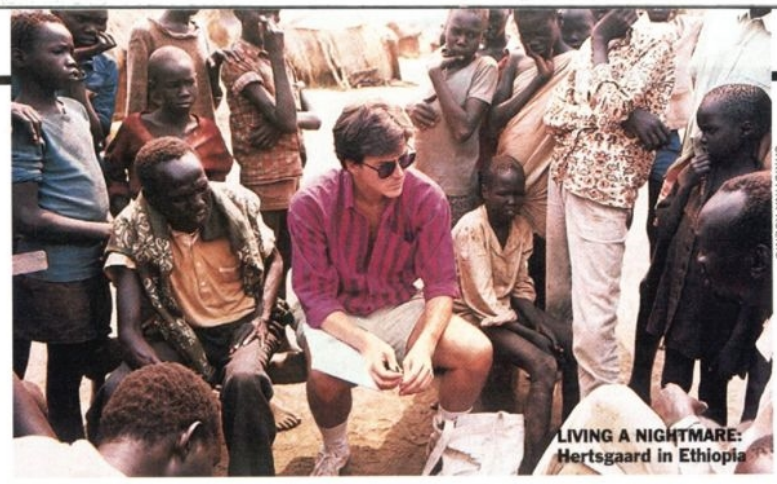
Elizabeth Strout tests the strength of that umbilical bond in her first novel, *Amy and Isabelle* (Random House; 304 pages; $22.95). In the small New England town of Shirley Falls, Isabelle Goodrow is a single mother with a shameful secret: her daughter Amy, 16, is illegitimate. As if in atonement for her youthful fling, Isabelle is now, in her early 30s, the image of propriety, maintaining perfect posture and an immaculate French twist. She craves respectability but is too poor for the upper echelon of Shirley Falls and too proud to befriend her co-workers at the mill. Amy shares her isolation, and an intense connection is born of their mutual dependency. Still, Isabelle yearns for more—her boss, sex, an existence outside the lonely one she shares with her child: she "could not bear to stop thinking that her real life would happen somewhere else."

JAMES KEYSER FOR TIME

FAMILY TIES: Strout probes the parent-child relationship in a moving first novel

It happens in a high school classroom when Thomas Robertson, a fortyish substitute math teacher, takes notice of Amy, who has inherited her mother's shyness but none of her plainness. When Robertson urges Amy to "come on out ... everybody's been asking about you," she complies in ways that she, and certainly Isabelle, never imagined.

Mother and daughter become rivals, and the balance of power between them shifts inexorably in favor of Amy as she, not Isabelle, discovers love. For Isabelle, it is painful recompense for what she considers a lifetime of sacrifice. Strout's insights into the complex psychology between the pair result in a poignant tale about two comings of age. Amy blossoms with a heady awareness of her sexuality. Meanwhile, Isabelle forgives herself the past, even as she faces its consequences: "It was bewildering to Isabelle. Bewildering that you could harm a child without even knowing, thinking all the while you were being careful, conscientious." Strout, with this assured debut, shows compassion for both. —*By Nadya Labi*



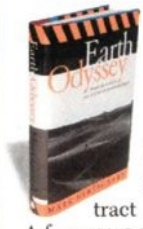
CHRISTINA KOENIG

LIVING A NIGHTMARE: Hertsgaard in Ethiopia

BOOKS

Travels on an Ailing Planet

An eco-conscious Marco Polo has sad tales to tell



TRAVEL WRITING INVOLVES an odd social contract: writer, for pay, agrees to view inspirational scenery and have a great time, saving reader the trouble of doing so. But Mark Hertsgaard's contract was odder than most. A few years ago, the journalist, who has written books on the Reagan Administration, nuclear energy and the Beatles, set off on a trip around the world in search of noxious vistas and pollutive sunsets—the environmental wreckage that other travelers take pains to avoid. His clear-eyed report, *Earth Odyssey* (Broadway Books; 372 pages; $26), backed by careful scholarship, is one of the best environmental books in recent years. It may help save readers the trouble of living through ecological decline and fall, if enough of them figure out how and where to apply its bitter lessons.

When Hertsgaard travels to western Ethiopia and sees starving Dinka refugees—tall and reedlike—there's not much to say except that life is cruel. They were driven from their home in Sudan by drought and war, and these are ancient, traditional plagues, not modern inventions. It is in Bangkok, strangely enough, that the message of Hertsgaard's journeying begins to strike home. This sprawling river city is like most others—mad about cars, paralyzed by car traffic, its air made unbreathable by cars and its municipal life dying of cars. If this were all, the moral would be simple: avoid Bangkok. Yet cars there, and across Europe and especially in the U.S., are efficient carbon generators. And carbon dioxide is the main ingredient in the greenhouse shield that is warming the globe and adding furious energy to epochal storms and floods.

China also lusts after cars, of course, and manufactures and imports as many as possible. Road building in China swallows scarce farmland, and traffic chokes streets and highways. Coal heats the chilly north, generates electricity and fouls the air. To Hertsgaard, big-shot capitalism seems a scourge—though not to the newly prosperous Chinese he meets, who brag that they get used to bad air. This single nation, the author observes, holds veto power over any environmental reforms the rest of the world may choose to try.

But so does the U.S., whose waffling on global warming Hertsgaard notes with contempt. He concludes his book, as is customary, with a spoonful of optimism. The marvelous energy of capitalism, he suggests, could be put to conserving energy. Insulate more; heat and cool less. Build green fridges and cars that run on nonpolluting fuel cells.

Sure. But environmental degradation, which is what Hertsgaard is asking readers to be worried about, is one of those vaguely irritating phrases that sink to the bottom of public discourse and stay there like sludge. The mind's response, after the 20th hearing, is a weary "Yeah, yeah." Got to get the kids off to school. Got to invest in a hog factory, build on a floodplain, send bigger boats after fewer fish. Write a check to Greenpeace. Buy Exxon Mobil. And be sure to pick up some bottled water. —***By John Skow***

A world of ideas on public policy.

Healthcare Reform: The Real Stakes.

By William C. Steere, Jr.

During the past two decades, all of the industrialised nations have enacted some form of healthcare reform. America is no exception. Just a few years ago, the U.S. was consumed by a vigorous public debate about healthcare. In the end, the debate was a useful one, reaffirming that the U.S. would retain its essentially market-based system. Instead of reform imposed from the top down, the American healthcare system underwent some rather profound self-reform, driven by powerful market forces. The market – not the government – managed to wring inflation out of the private healthcare market.

Today, it appears that U.S. healthcare costs are again on the rise. At the same time, American patients – like patients elsewhere – are becoming more vocal about the restrictions many face in their healthcare plans. Talk of government-led reform is once again in the air.

We must think twice, though, before embarking on "reform" if that means imposing further restrictions on our healthcare markets. The more sensible course is to introduce policies that make the market work better – that is, to the advantage of consumers. I base this argument on our company's decades of experience in healthcare systems around the world, which has given us a unique global perspective on the right and wrong way to reform healthcare. The wrong way is to impose layer after layer of regulation and restrictions. We have seen this approach tried in many countries, and we have always seen it fail – fail to hold down costs, and fail to provide the best quality care. Medicine is changing at so rapid a pace that no government agency or expert commission, however learned, can keep up with it. Only an open, informed and competitive market can do that. This lesson holds true for the U.S. and for all countries contemplating healthcare reform. Free markets do what governments mean to do - but can't.

The right approach is to foster a flexible, market-based system in which consumers have rights, responsibilities, and choices. Healthcare systems do not work if patients are treated as passive recipients of services; they do work if consumers are well-informed about quality, costs, and new treatments, and are free to act responsibly on that knowledge.

Reform should never be driven purely by cost considerations. Instead, we ought to devise new ways of funding healthcare that will make it possible for all patients to afford the best care. Ideally, these new approaches would reward individuals and families for saving and investing in their own healthcare. They would also encourage innovation, which can make healthcare systems more efficient, more productive, and ultimately of greater value for patients.

The path we choose will have enormous implications for all of us. We are in a golden age of science, and no field of scientific inquiry holds more promise than that of biomedicine. Not only can we look forward to the discovery of cures for chronic and acute diseases, but also to the development of enabling therapies that can help people enjoy more rewarding and productive lives. New drugs are already helping people who would once have been disabled by arthritis or cardiovascular disease stay active and mobile. More effective anti-depressants and anti-psychotics are beginning to relieve the crippling illnesses of the mind, allowing sufferers to function normally and happily in society. The promise is – quite simply – one of longer, healthier lives.

What is at issue are the pace and breadth of discovery, and how quickly we can make the benefits of our knowledge available to the patients who need them.

> ***No field of scientific inquiry holds more promise than that of biomedicine***

That is the task of companies like ours. However brilliant the basic research behind a new therapy, it takes the resources and capabilities of a pharmaceutical company to discover, develop and ensure broad awareness of a new medicine.

Therefore, the policy environment the industry will face in the next century may make or break the next wave of biomedical breakthroughs. Will that environment include protection for intellectual property, freedom for the market to determine price, and support for a robust science base? Will healthcare systems nurture innovation, or remove incentives for discovery? Will they give consumers information and options, or impose stringent rules and regulations that limit access and choice? For the U.S., as for the rest of the world, the healthcare debate is by no means over. And for all of us, the stakes are higher than ever.

William C. Steere, Jr., is Chairman and CEO of Pfizer Inc.

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WOMEN'S HEALTH

We're Pfizer. We're committed to reminding women to care for their own health. We're getting the word out that heart disease is the leading cause of death among women. Educating women that as many as 1 in 4 of them are likely to experience depression. Opening eyes to the debilitating effects of migraines. Helping women understand how their family history affects their own likelihood of illness. At Pfizer, health is most definitely a women's issue.

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EXHIBITS

THE METROPOLITAN MUSEUM OF ART

CUBISM AND FASHION ***The Metropolitan Museum of Art*** How did women's dress evolve from the balloon-derrière silhouette of the 19th century to the cleaner, linear look that has characterized the 20th? This show at the Met's Costume Institute makes the dazzling and utterly convincing visual argument that what facilitated the transition was the influence of Cubist painting and theory. From the tunics of Callot Soeurs to the cylindrical day dresses of Vionnet to the drop-waist skirts of Chanel in the 1920s, fashion's deflation followed the Cubist embrace of the plane. In other words, liberated from corsets, women everywhere owe a thank-you to Picasso and Braque. *—By Ginia Bellafante*

TELEVISION

CLASSIC ARTS SHOWCASE It's 1954, and the young Patrice Munsel, sounding as ravishing as she looks, is singing an aria from Charpentier's *Louise*. Suddenly it's 1986, and members of the Bolshoi Ballet are dancing an exuberant pas de deux. H.G. Wells' time machine? No, *Classic Arts Showcase:* MTV for gourmets. The commercial-free service can be hard to find—it airs at odd hours, mostly on PBS or public access cable channels—but the search yields a feast. Opera, dance, chamber music, theater and more are presented in a beguiling spread of video clips. So surf that dial, comb that *TV Guide*. Caruso and Domingo, Lillian Gish and Paul Robeson, the Canadian Brass and James Galway all await. *—By William Tynan*

BMG CLASSICS

THE SOPRANOS ***HBO, Sundays, 9 p.m. E.T.*** When it comes to TV depictions of Mob life, we know we can count on the fact that men will get whacked, women will wear unflattering housecoats and someone at some point will say "prosciutt'." What we don't expect is to follow a wiseguy's path through psychotherapy. Debuting on Jan. 10, this wryly conceived weekly drama focuses on Anthony Soprano (James Gandolfini), a suburban dad and Mafioso whose general malaise and thorny mommy issues send him to the couch. While refraining from slapping the comedy on too thick, creator David Chase has made Soprano's inward search surprisingly affecting. Soprano may not have Ally McBeal's legs, but his introspection is a lot more fun to watch. *—G.B.*

ANTHONY NESTE—HBO

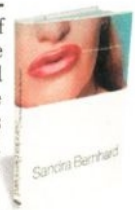
PROGENY WATCH

MIRANDA PENN TURIN—WARNER BROS. RECORDS

MONICA MANCINI: On her eponymous debut album, Henry Mancini's daughter reveals a strong but sweet voice that rides a melody just so. The songs are Dad's—*Moon River* and others—with their mix of sophistication and schmaltz. Tart strings help keep Monica on the right side of the equation. The new label is PBS Records: music to drive Volvos by? *—By Bruce Handy*

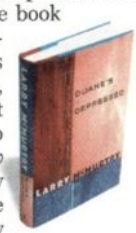
BOOKS

MAY I KISS YOU ON THE LIPS, MISS SANDRA? ***By Sandra Bernhard*** This collection of random musings from the monologist-actress and chic wit again makes the case that Bernhard's brand of observational humor is like no one else's. In her new work, Bernhard draws on her boundless imagination to pay homage to her housepainter, Jewish mysticism and Brenda Vaccaro while conjuring up ad campaigns for Mother Teresa–inspired day wear. Do we mind that Bernhard's reflections can be a bit too solipsistic, a bit over the top? Nope. *—G.B.*



Sandra Bernhard

DUANE'S DEPRESSED ***By Larry McMurtry*** The title, a sly gibe at John Updike, *Rabbit at Rest* and all the other *Rabbits*, is worth a smile. Here, McMurtry's Duane Moore, 62, rich, beset by family and bored to a frazzle, flummoxes his Texas town by ditching his pickup truck and walking everywhere. The book is within cat-kicking distance of funny. Real guys don't walk, not in Thalia, Texas. The trouble is that Duane, wambling hero of *The Last Picture Show* and *Texasville*, is actually becalmed. He has lost the happy soul's gift of reality avoidance. So too with McMurtry, usually an inspired melodramatist, who plays this one so straight and flat that neither he nor his hero can find any curative trouble for Duane to get into. The poor fellow needs a buffalo stampede or a seductive IRS auditor, but nothing turns up. *—By John Skow*



MUSIC

BELEZA TROPICAL 2: NOVO! MAIS! MELHOR! ***Various Artists*** When Western pop performers draw explicitly from Third World sources, one can get the queasy feeling that somewhere an indigenous artist is producing better, more authentic music that will never be widely heard. In this compilation, rocker David Byrne plays it cool, stands back and simply presents the original work of some of his favorite Brazilian artists. The album draws on samba as well as psychedelic rock and '90s clubland rhythms. It's all a lot of fun, though one wishes it could, at times, be a little less lighthearted. Listeners searching for more depth should check out last year's *Nova Bossa: Red Hot* on Verve, a collection of Brazilian pop drawn mostly from the '50s and '60s. It's a treat of an album—and moving to boot. *—By Christopher John Farley*

PHYLLIS GALEMBO—LUAKA BOP

Daniel Kadlec

Stealth Tax Hikes

Tax cuts got lots of ink, but the overall tab will rise this year; here's why—and what you can do

A COMMON MISCONCEPTION IS THAT TAXES ARE GOing down. Sorry, it just isn't so. True, some tax rates have fallen. And tax reform last year gave us tax credits for education and tax deductions for long-term savings. But new targeted breaks total maybe $20 billion, which pales next to Americans' annual tax burden of nearly $3 trillion. In 1998 it took the combined incomes of everybody in the U.S. through May 10 to pay all taxes owed for the year—the latest "tax freedom" day ever, says the Tax Foundation, which figures the date will be even later this year.

That's not all bad. A prosperous economy leads to more personal income, which shoves more taxpayers into higher tax brackets, so they owe more in taxes. Thus the taxpayer burden may grow faster than income, and taxpayers still get ahead. That's the way our progressive tax system works: the more you make, the higher your tax rate. But it is one of the hidden ways taxes are on the rise. Here are some others, and what to do about them:

Rising FICA burden. Beginning this year, you will pay Social Security tax on the first $72,600 you earn—up from the $68,400 threshold in 1998. That's a 6.1% hike, a rate that is roughly double the pay increase most wage earners will see. For anyone whose income exceeds that higher level, it means an extra $260.40 a year owed to the feds. Tip: earnings stashed in a flexible-spending account at work are exempt from FICA withholding. In a two-earner household, it may pay for the lower earner to fund the account.

Alternative minimum tax. Designed to afflict only the superrich, this monster increasingly soaks the middle class. More than 1 million taxpayers will owe it this year, and 9 million by 2008—including many earning considerably less than $100,000 a year. Little more than a decade ago, fewer than 100,000 people were subject to the AMT. It's a complicated tax that targets folks who avoid most traditional income taxes through large credits and deductions. High earners in high-tax states are most vulnerable, but anyone taking a large deduction for business expenses can fall victim. Tip: consult a pro. Avoiding the AMT may call for such radical action as accelerating income and deferring deductions, which is precisely the opposite of normal strategy.

No-See-'em Taxes

- **Social Security** will take the same 12.4%—but out of more pay
- **Alternative minimum tax,** designed to soak the rich, plagues the middle class now
- **Mutual funds** that decline may still distribute taxable gains

Mutual fund taxes. Heaping insult on injury, many investors owe 1998 tax on capital gains recorded by their mutual funds, even if those funds lost money. More than 30% of stock funds were down through November, and 11% of those—including such popular funds as Heartland Value, Lindner Dividend, Brandywine and Templeton Growth—also distributed a taxable capital gain to shareholders, says fund-research company Wiesenberger. Tip: taxable distributions typically result from rapid-fire trading. This year, look for funds with a low turnover rate, something less than 100%. Stock index funds are among the most tax efficient. And never invest in a stock fund just ahead of its annual distribution, usually in November or December.

Roth conversion. Moving from an old IRA to a Roth IRA can trigger unexpected tax consequences. The additional income recorded during the conversion year may result in fewer itemized deductions. That's even more likely now, since last year's one-time opportunity to spread the income over four years has expired. Tip: converting to a Roth still makes sense for the young, as it does for older folks who won't need to tap their IRAs for daily expenses. ■

See **time.com/personal** *for more on taxes. E-mail Dan at* **kadlec@time.com.** *And see him on CNNfn Tuesdays at 12:45 p.m. E.T.*

Costly Calling-Card Calls

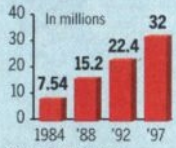
LAW-ENFORCEMENT OFFICIALS ARE investigating a new phone scam in which hackers electronically steal calling-card numbers from travelers. As he prepares to make a call, the victim hears a pay phone ring in an airport and answers it, only to find no one on the line. But when he then dials his own call, the crooks tap in and swipe his card number. A tip to the curious: pick up, then hang up for 20 seconds before dialing.

JOHN F. MASON—THE STOCK MARKET

Early Entrée to a 401(k)

FOR NEW HIRES EAGER TO SOCK MONEY away in a 401(k) plan, the wait may be over. Thanks to a change in tax regulations taking effect this month, companies no longer have a financial incentive to make new employees wait up to a year before becoming eligible for these tax-deferred savings plans. Some 70% of firms impose a waiting period; ask your new boss about reaping the benefits now.

Growth of 401(k) participants

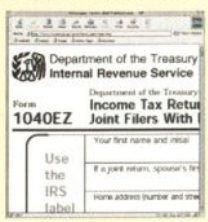


Source: Profit Sharing Council of America

Paperless Tax Payments

FILING INCOME TAXES VIA PC ISN'T A seamless transaction; after slaving away at the keyboard, you still have to sign the old-fashioned way. But in a pilot program this year, a few million e-filers who have software like TurboTax, as well as those who use a preparer like H&R Block, can zap their 1040—paper free—with a code substituting for their signature. E-filers can also pay their balance due by phone with a credit card—for a fee, of course.

—By Daniel Eisenberg



Christine Gorman

Try, Try Again

Another year, another chance to make your New Year's diet and exercise resolutions stick

IF YOU'VE MAINTAINED YOUR WORKOUT SCHEDULE during the past few weeks of holiday madness, kept your cool while flagging down salesclerks and passed on the chocolate-covered treats at the office, then you have my sincere congratulations. But if you're like the rest of us, you've slept in, lost your temper and scarfed down the cookies. So now, like millions of other Americans, you have made yet another New Year's resolution to drop a few pounds, exercise more, drink less, stop smoking or just plain chill out.

It won't be easy. In fact, you may have already broken the resolution you made last week. But if you're willing to try again, here's a list of tips to improve your chances of success:

Set realistic goals. If you're 50, 30 or 20 lbs. overweight, don't even think about losing them before Valentine's Day. It's not only unlikely but unhealthy as well. A good rule of thumb is no more than a pound or two a week.

Don't try to do everything at once. This one can be tough, especially if you need to lose weight, because your best hope for long-term success requires permanent changes in your diet as well as a boost in your physical activity. But improvements in one area often lead to changes in others. If you're exercising regularly, for example, you're likely to find yourself eating more healthfully as well, so as not to undermine your "investment."

Find a buddy who shares your goals. You can encourage each other during the tough times and tackle new adventures together. My jogging partner signed us up for a 5-km run at midnight, God help us, in Central Park on New Year's Eve. The mere thought of it kept me pounding the pavement these past few weeks.

Don't be afraid to ask for professional help, especially if you're tackling alcoholism, drug or nicotine addiction.

Be specific about how you're going to keep your resolutions. Instead of vaguely promising "to exercise more," decide to take a 30-min. walk at lunchtime three days a week. Or instead of saying you'll eat less fat, make up your mind to bring your lunch to work. (By the way, you don't have to condemn yourself to carrots and celery sticks only. Just preparing your own food can cut hundreds of calories from the typical American diet.)

Record your progress. Jotting down how many miles you walk or the number of pounds you bench-press each week provides a sense of accomplishment and is a great motivator. It can also help you identify potential trouble spots in your routine.

Accept your limitations. A lot of us get hung up on the idea that we have to reform perfectly or not at all. We floss our teeth twice a day every day for a week, then we forget one morning and give up trying for the rest of the year. Let's face it. You're going to suffer setbacks. Be honest with yourself about why they happened, then pick up the pieces and move on.

Learn new coping skills. Stress is the No. 1 reason that ex-smokers relapse. Stress is inevitable. But you can blunt its effects by meditating, exercising or rehearsing ahead of time your ideal response to an anxious situation.

So now that I've made it out of Central Park alive, what have I resolved to do in 1999? I've got to admit, those vegetables are still nagging at me. Now that I've tried some of the 30-odd recipes readers have sent me for Brussels sprouts, I'm looking for a couple of good ones for bok choy. ■

For more Web resources on New Year's resolutions, visit **time.com/personal.** *You can e-mail Christine at* **gorman@time.com**

RICK NEASE FOR TIME

Good News on Hormones

THIS IS SWEET: THE FDA HAS okayed an all-natural progesterone derived from Mexican yams for use, along with estrogen, in hormone-replacement therapy. Called Prometrium, it's identical to progesterone in a woman's body. As a side benefit, it raises good cholesterol more effectively than today's synthetic progesterones.

Bad News on Smoking

WARNING: CIGARETTE SMOKING MAY BE hazardous to your … marriage? Well, yes. New research finds smokers are 53% more likely to divorce than nonsmokers. Granted the filthy habit is a turnoff, but the real reason behind the breakups may be that smokers are more likely to suffer from problems like depression and anxiety—which can shake up any marriage.

Good News on Arteries

TWO REPORTS SUGGEST THAT NEW NONinvasive techniques can detect blocked arteries before a heart attack occurs. In one study, scientists used an ultrafast C.T. scan and computer technology to view and monitor plaque. In the other, researchers successfully used the scan with an injectable dye to see if arteries had actually narrowed. One conventional method, the stress test, isn't always reliable; in angiograms, the other technique, a catheter must be threaded to the heart.

Bad News on Drinking

ARTHUR BECK—THE STOCK MARKET

THREE-MARTINI LUNCHES are out, but workers are still imbibing—occasionally. Some 23% of managers sometimes have a drink during the workday, and 25% of all workers occasionally come in with a hangover. Why care? Researchers now think casual drinking is a big cause of absenteeism, tardiness and poor productivity. —**By Janice M. Horowitz**

Sources: FDA; *Families, Systems & Health*; *New England Journal of Medicine*; Robert Wood Johnson Foundation

Joshua Quittner

I Get Mail!

And the subjects range from the technologically sublime to the sociologically ridiculous

I AM DOOMED TO LIVE AMONG THE MONIMALS. AS readers of this column know too well, Monimals are furry, decorative computer-monitor covers. With one, you can gussy up your screen so it looks like a cow, for instance. Or a moose. Whatever. I can't ignore the wretched things. The No. 1 question among Personal Technology readers? "Where can I get one?" The blurb we ran about Monimals some months ago gave its website (*www.monimals.com*) as the sole point of contact. Tragically, the site doesn't tell you where to buy one in the U.S. And, until recently, I couldn't answer your questions. Then, a month ago, kismet. I was at a sushi bar in the middle of the desert (Las Vegas) listening with approval as the Brit on the stool next to me browbeat the chef: "It tastes like a black plastic bag," he whined, pointing to his tuna roll. "I can't eat the bahhhg-tasting thing!" Figuring he was a fellow critic, I struck up a conversation. The man turned out to be Joe McAllister—CEO of Monimals Trading Co. Ltd. of London! "Where can you buy those damn things?" I asked. It was the beginning of a beautiful friendship that has at last allowed me to answer the biggest question of our TIME: You can find Monimals at the Electronic Boutique chain. Or call 1-800-948-6777 to order direct.

Want one?

To find out where to get your own Monimal, you can try going to **www.monimals.com.** Or you can hang out in Las Vegas sushi bars and hope you meet the company's CEO

When I started writing this column last summer, I assumed I'd get more questions about stuff like Monimals than, say, the vagaries of 3-D accelerators. And, frankly, it's a relief: Millions of people are buying computers for the first time, and the advice they seek tends to be on the practical (if not whimsical) side. There are a lot of beginners out there. For instance, every week I point people to our website, *timedigital.com*, for more information about the column's topic. Invariably, I get e-mail from readers saying something like: "I tried to look up timedigital.com, but I got thousands of hits. Which one is your page?" Aha! I snort. Here's a person who is still confused about the difference between a browser and a search engine! (Don't be ashamed. I have an editor who is also befuddled on this point.) Think of a browser as the 3-D glasses your computer needs to "see" things on the Web. When you launch the program and type in an address, you can visit Web pages on the Net. And the most popular places people visit are search engines; they archive the hundreds of millions of pages that make up the World Wide Web. Yahoo, Excite, InfoSeek, Lycos and Hotbot are examples of search engines. The confusion probably stems from the fact that Netscape's and Microsoft's browsers (the Coke and Pepsi of the browser market) take you to their own home pages—which have search engines—when you start them. You can change that start page by going to the browser menu's "Internet options" on a PC or "Preferences" on a Mac.

Finally, I admit that I get a fair number of questions about 3-D accelerators. These devices help your PC display three-dimensional graphics. But unless you play the latest and greatest games on your PC, you really don't need one. You can spend many hundreds of dollars, which I wouldn't recommend for anyone but graphic artists. I've tried most of them and can't see a difference, frankly. So my advice to gamers is to spend as little as possible. Now, the choice between a cow and a moose Monimal, though, is something we can discuss. ■

If you have reasonable—and maybe even unreasonable—questions for Josh Quittner, he can be reached at **jquit@well.com.**

RICK NEASE FOR TIME

Don't Surf, Ride!

HARLEY-DAVIDSON FANS WHO ARE moving their hands away from the throttle and onto the mouse worry M.Z. Berger & Co., maker of Harley watches. So the company plans to lure the riders away from computers and back to bikes. Those who send in their computer mouses will be rewarded with watches and other Harley apparel. No word yet on free tattoos.

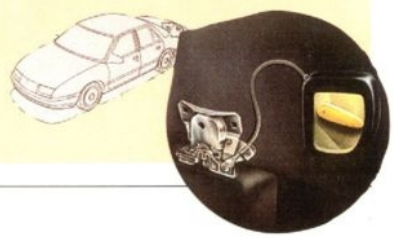
LISA QUINONES—BLACK STAR

Virtual Clerk

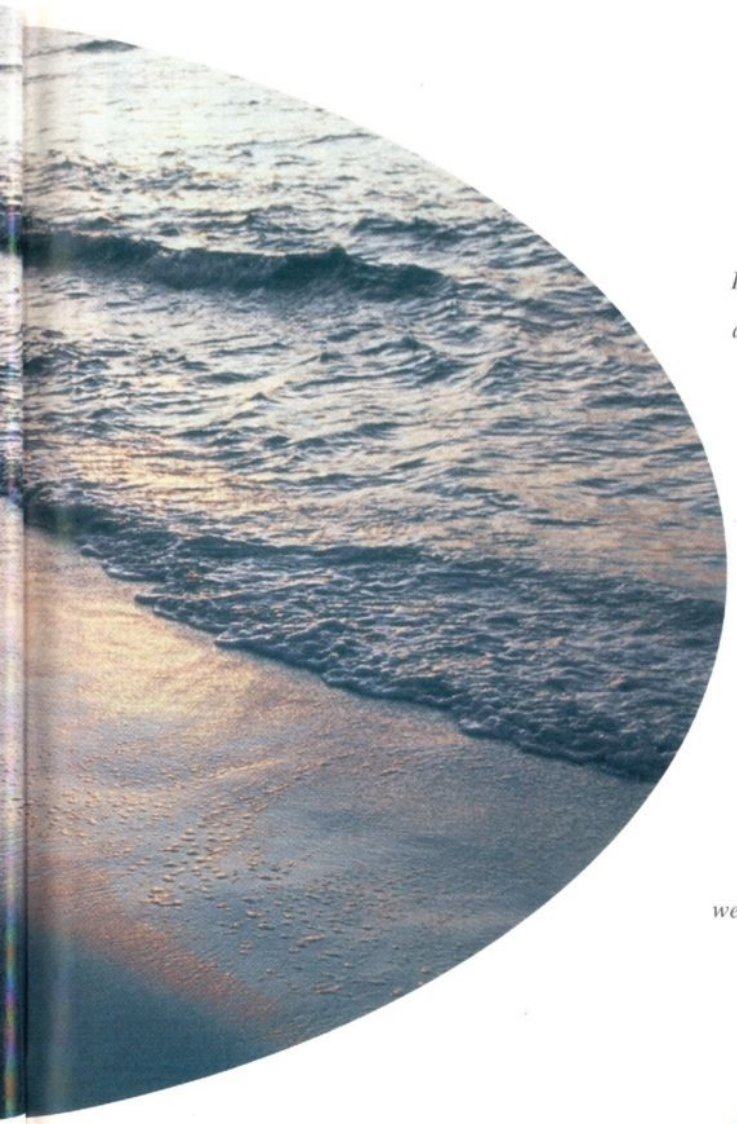
IF YOU'RE SICK AND TIRED OF TRYING to pry the local video-store clerk's attention away from *Austin Powers* to your movie needs, help is on the way. ObjectSoft's FastTake video kiosk, coming to video outlets this month, lets you search a retailer's listings by title, actor, director, rating or genre. The computer will suggest films you might like—and won't sneer at your choices.

A Safer Trunk

LAST SUMMER ALONE, 11 CHILDREN died in the U.S. because they locked themselves inside car trunks while playing. In response, General Motors has developed a child-resistant trunk kit that contains an illuminated yellow escape handle. A latch must be reset manually for the trunk lid to close, and a strap prevents kids from entering the trunk through the backseat. The $50 package can be installed by a dealer on most 1990 or newer GM cars. —**By Rebecca Winters**



We help people love one another.



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We spend over two billion dollars a year on research. In the process, we discovered a treatment for a disease that affects the lives of millions of men and their partners —erectile dysfunction. Today, we believe we'll introduce more new medicines for more diseases than anyone else. Rest assured, at Pfizer, we're not just looking for cures for the future, we're determined to find them.

ERECTILE DYSFUNCTION

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Most men will have an isolated erection problem at some time in their lives, but for others it happens more frequently. If the inability to respond naturally to your partner has become a recurring problem, you may be suffering from a treatable medical condition called erectile dysfunction (ED), also known as impotence. The following questions and answers are designed to give you a brief introduction to the causes of ED and the various treatment options available. If you believe you are suffering from ED, or want to know more about the condition, talk to your doctor or other healthcare professional.

Erectile dysfunction: what every man should know

What is ED?

Erectile dysfunction is the consistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity. That means not just an occasional problem, but one that has been occurring repeatedly for a period of time. It's a widespread condition, shared by approximately 30 million men in the United States.

What causes ED?

It was once believed that ED is all in your head, or just an inevitable result of getting older. Actually, the majority of ED cases are associated with physical conditions or events, including some that are age-related. The most common risk factors for ED include:

- *Diabetes, high blood pressure, hardening of the arteries, or high cholesterol*
- *Injury or illness, such as spinal cord injury, multiple sclerosis, depression, stroke, or surgery for the prostate or colon*
- *Medications that may bring about ED as an unwanted side effect*
- *Cigarette smoking or alcohol/drug abuse*
- *Psychological conditions, such as anxiety and stress*

If you want to know more about ED, talk to your doctor.

Can erectile dysfunction be treated?

Yes. The good news is that, regardless of the cause, the vast majority of ED cases are treatable. Patients have a variety of treatment options from which to choose, including oral medication, hand-held vacuum pumps, self-administered injections, pellet suppositories, and surgical implants.

Can anyone use these treatments?

It's important to remember that these treatments are not for everyone, but only for men diagnosed with ED. You and your doctor can determine the appropriate treatment for you. Because sexual activity can be demanding on the heart, you should talk to your doctor before using any treatment for ED.

How do I know if I have ED?

If you have erection problems, you probably already know it. But before your condition can be treated, you need to be diagnosed by your doctor. There is no need to be embarrassed or ashamed when discussing ED with your doctor. He or she has probably diagnosed and treated ED many times. Your doctor can provide you with understanding, support, and best of all, information.

To diagnose ED, doctors typically ask a few specific questions and give a routine physical exam. This should help your doctor arrive at a diagnosis. Before starting any treatment for ED, ask your doctor if your heart is healthy enough to handle the extra strain of having sex.

Based on this information, you and your doctor will decide on the treatment that is best for you.

REMEMBER:

ED is a common medical condition.

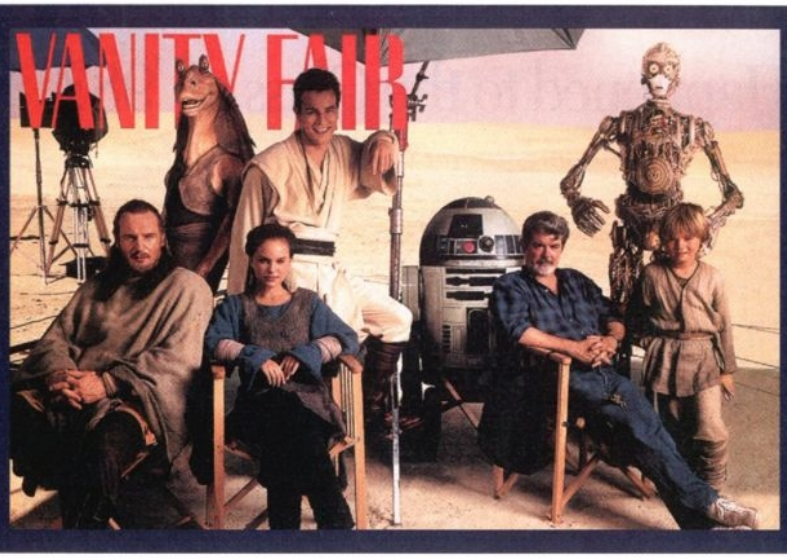
It's not an inevitable result of growing older.

ED is treatable with a variety of methods.

Only your doctor can prescribe the appropriate treatment.

By MICHELE ORECKLIN

ANNIE LEIBOVITZ—VANITY FAIR



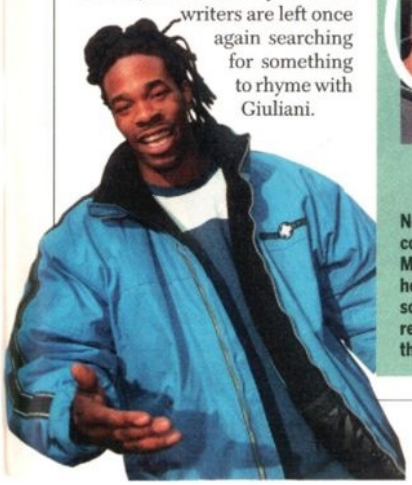
EVERYONE SMILE AND SAY "YODA"

That face in the upper left-hand corner may look a lot homelier than those *Vanity Fair* normally features on its cover, but you can bet your Tatooine the magazine recognized his undeniable appeal to stalwart *Star Wars* fans everywhere. On its new issue, due early this month, *Vanity Fair* features this cover photograph by Annie Leibovitz, who was granted exclusive access to the superfluously secretive Tunisian set of the *Star Wars* prequel *The Phantom Menace*. From left, LIAM NEESON as Jedi Knight Qui-Gon Jinn; the ugly guy (known as Jar Jar); NATALIE PORTMAN as Queen Amidala, mother of Luke and Leia; EWAN MCGREGOR as a young Obi-Wan Kenobi; R2-D2; director GEORGE LUCAS; C-3PO; and JAKE LLOYD, here as the still angelic Anakin Skywalker, but better known as the future Darth Vader.

What the Dilly?

The arrest of hyperfrenetic rapper **BUSTA RHYMES** in New York City last week fueled the imagination of pun-happy journalists, who showcased their wit with such headlines as BUSTA BUSTED, BUSTA CRIMES and BUSTED RHYMES. Police had observed the singer driving erratically in Manhattan, pulled him over and found a loaded, unregistered pistol in the back seat as well as a small amount of marijuana in the pocket of Busta's manager and passenger, Gerald Odom. Both men were charged with possession of a weapon; Odom was also charged with possession of marijuana. Released on their own recognizance, the two will return to court later this month; meanwhile city headline writers are left once again searching for something to rhyme with Giuliani.

TAMARA BECKWITH/NY POST—CORBIS



URBANO DELVALLE

Kids, Can You Spell G-U-N?

MISTER ROGERS has finally found a neighbor he'd like to run out of town. Gadzooks, Inc., a Texas-based company, has been selling T shirts of the preternaturally placid TV host packing heat and daring neighbors to enter his "hood." As Fred Rogers is loath to suggest that he has ever strapped on a holster beneath his well-worn cardigan, his company, Family Communications, Inc., is suing Gadzooks, alleging that the T shirts violate Rogers' privacy and wrongly benefit from his image. Plus, says his lawyer, "it's bad for the kids." A spokesperson for Gadzooks says the offending apparel has already been cleared from the shelves. Let's hope the whole thing blows over before Captain Kangaroo goes postal.

ERICKSON, MARK LENNIHAN—AP; RHODES, DAN HULSHIZER—AP; MARCHIBRODA, BETH KEISER—AP; WANNSTEDT, MICHAEL GREEN—AP; CAPERS, RICK HAVNER—AP

NFL SETS NEW SACK RECORD

Not even Quentin Tarantino produces this many corpses. Monday-morning quarterbacking gave way to Monday-morning desk clearing last week when five NFL head coaches were fired even before the regular season ended, setting one of the league's more inglorious records. The Seattle Seahawks' DENNIS ERICKSON, the Philadelphia Eagles' RAY RHODES, the Baltimore Ravens' TED MARCHIBRODA, the Chicago Bears' DAVE WANNSTEDT and the Carolina Panthers' DOM CAPERS were all unemployed by Monday night. With heads rolling like loose balls, an expansion team set to debut and more coaches on shaky ground, 11 positions may need filling for next season. Say, those NBA coaches haven't been doing much lately ...

Bruce Handy/Alan Reingold

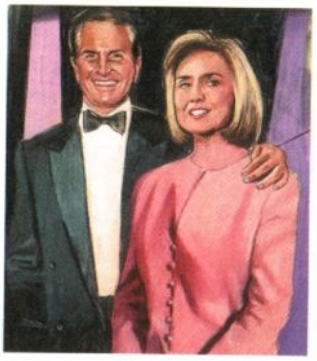
What Ever Happened to the Class of '98?

Fifth-Year-Reunion Alumni Notes

Linda reports she's still at the Pentagon and hopes someday to "have lunch with a co-worker. But I'm not bitter (*ha-ha*)"

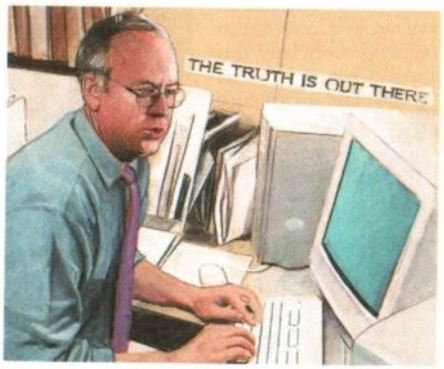
Monica—like she can't stop *telling* everyone—is starring in the new John Waters movie (but not for DreamWorks!). Co-star Patty Hearst "is like my second mom"

Bill writes from Hollywood that he was "saddened but not bowed" by the box-office performance of *Prince of Hyannis Port*. He is proud that the movie's love theme—*Flawed (Though Still in History's First Tier)*—was a hit for Brandy



Hillary—Senator Rodham to you!—says she's enjoying "the challenges and rewards of the single life"

Newt and "anywhere from six to more than two dozen followers" (as the papers say) were last reported in Montana



Ken is still living in Washington but says he hopes to move to Malibu "just as soon as the investigation is complete"

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